

Towards the Total Synthesis of Anthraquinone Antifungal Agents Sch 47554 and Sch 47555

A thesis submitted by

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In partial fulfilment of the requirements for the degree of

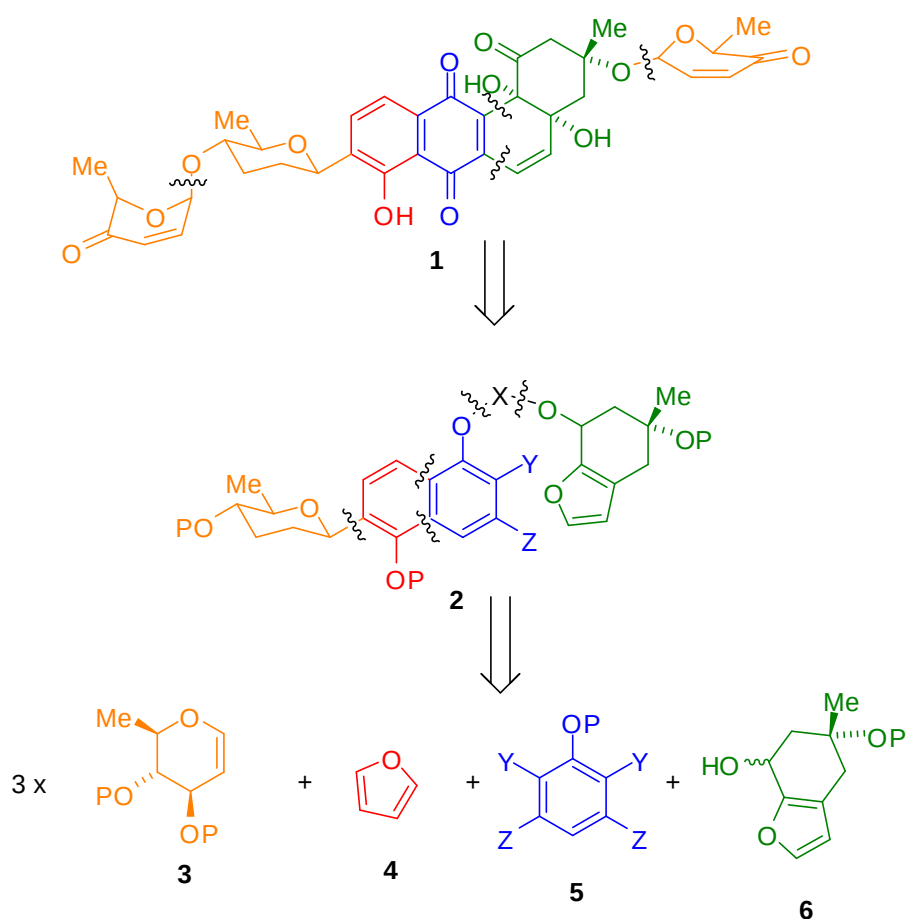
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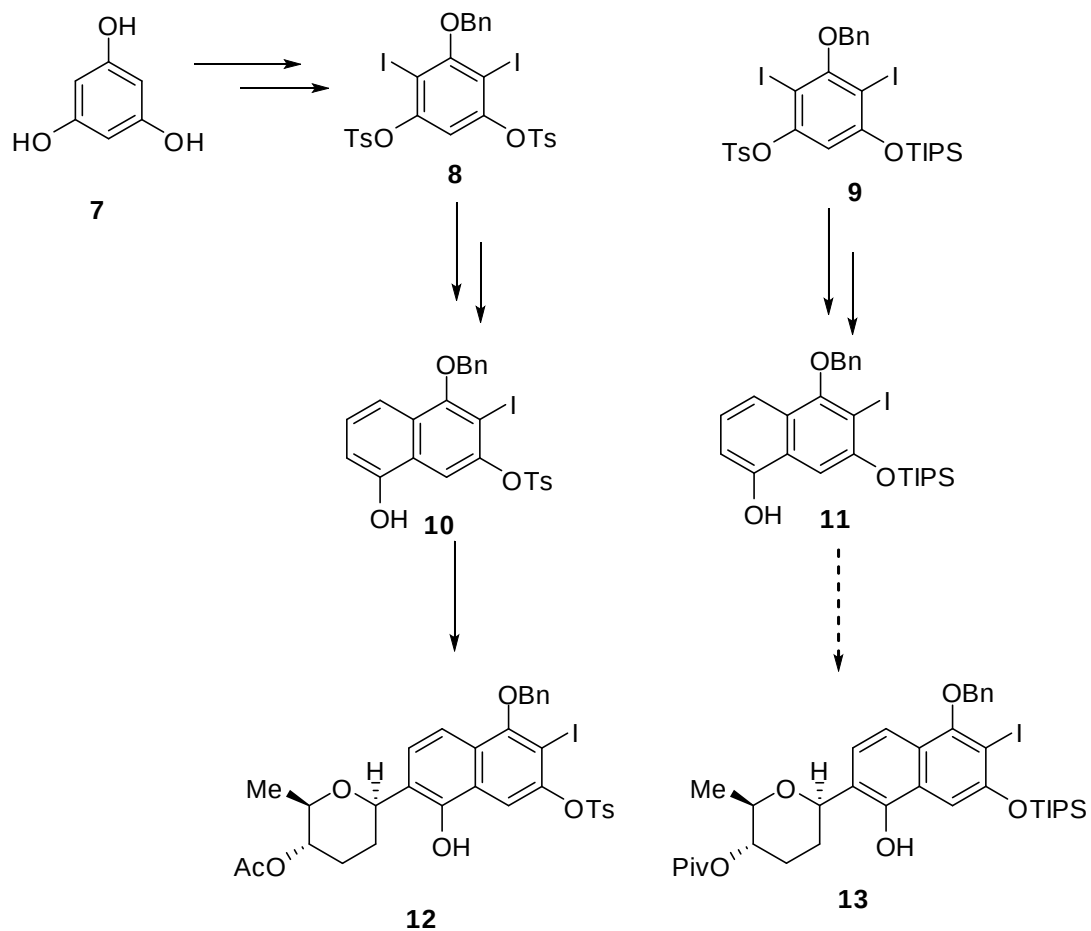
Abstract

The total synthesis of Sch 47554 (**1**) is the focus of this project, with the intention of using two aryne-furan cycloaddition reactions to efficiently build the anthraquinone core of the molecule. The first is intermolecular with furan, which is then elaborated with a C-aryl glycosidation reaction. The second is intramolecular between **5** and **6** where the two fragments are linked by a disposable tether connected through the oxygen functionalities, as demonstrated in **2**. This ensures the correct angularly-fused regiochemistry of the aryne-furan cycloaddition.



To this end suitable precursors have been examined. After several unsuccessful attempts at making various suitably-functionalised precursors, double aryne precursor **8** was synthesised and converted into naphthol **10**. This was successfully glycosylated, but this substrate is less flexible later in the synthesis than another

substrate developed, **9**. This was converted into naphthol **10** and the glycosidation is currently being optimised. Elsewhere in the group furan **6** has been synthesised. These systems are appropriate for completing the synthesis of **1**.



Acknowledgements

Firstly, I would like to thank Professor Tony Barrett for the opportunity to work in his group, his advice, encouragement and providing an environment where I have had the chance to learn and develop my skills. And of course for the parties! In that regard, a massive thank you to Katie M., Mickie and Sam for their assistance, organisation and other admin stuff.

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Abbreviations

ABCN	1,1'-azobis(cyclohexanecarbonitrile)
Ac	acetyl
Ar	aryl
BBDI	1- <i>tert</i> -butoxy-2- <i>tert</i> -butoxycarbonyl-1,2-dihydroisoquinoline
Bn	benzyl
<i>i</i> -Bu	<i>iso</i> -butyl
<i>n</i> -Bu	<i>n</i> -butyl
<i>s</i> -Bu	<i>sec</i> -butyl
<i>t</i> -Bu	<i>tert</i> -butyl
CI	chemical ionisation
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	dichlorodicyanoquinone
DEAD	diethyl azodicarboxylate
DIAD	di- <i>iso</i> -propyl azodicarboxylate
DIBAL-H	di- <i>iso</i> -butylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
DTAD	di- <i>tert</i> -butyl azodicarboxylate
Elem. Anal.	elemental analysis
ESI	electrospray ionisation
Et	ethyl
F-TEDA	1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate
GC	gas chromatography
Hz	Hertz
<i>i</i> -Pr	<i>iso</i> -propyl
IR	infrared
<i>J</i>	coupling constant

KHMDS	potassium hexamethyldisilazane
LDA	lithium di- <i>iso</i> -propylamine
LTMP	lithium tetramethylpiperidide
M	molar (mol.dm ⁻³)
MCPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
MMPP	magnesium monoperoxyphthalate
MOM	methoxymethyl
mp	melting point
MS	mass spectrometry
MTBSTFA	<i>N</i> -methyl- <i>N</i> - <i>tert</i> butylsilyldimethyltrifluoroacetamide
<i>m/z</i>	mass/charge
NBS	<i>N</i> -bromosuccinimide
NFSI	<i>N</i> -fluorodibenzenesulfonimide
NIS	<i>N</i> -bromosuccinimide
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
NMR	nuclear magnetic resonance
Piv	pivaloyl (trimethylacetyl)
PMB	<i>para</i> -methoxybenzyl
PTSA	<i>para</i> -toluenesulfonic acid
R _f	retention factor
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	<i>n</i> -tetrabutylammonium fluoride
TBAI	<i>n</i> -tetrabutylammonium iodide
TBAT	<i>n</i> -tetrabutylammonium triphenyldifluorosilicate
TBS/TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	tri- <i>iso</i> -propylsilyl
TLC	thin layer chromatography
Tf	trifluoromethanesulfonyl (trifyl)
Ts	<i>para</i> -toluenesulfonyl (tosyl)

TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
UV	ultraviolet

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Chapter 1: Introduction - Sch 47554, Sch 47555 and Angucycline Antibiotics

1.1 Sch 47554, Sch 47555 and Angucycline Antibiotics and their Biological Relevance

In the field of medicine there are many areas of disease which cause concern, but one which is often overlooked is that of fungal diseases. Species such as *Candida albicans*, *Cryptococcus neoformans*, *Pneumocystis carinii* and *Aspergillus fumigatus* often exist with no harmful effects to healthy patients, but can become pathogenic and cause serious problems regarding levels of morbidity and mortality in immunocompromised patients (e.g. those with AIDS or those having undergone chemotherapy or organ and bone marrow transplantation).¹ Furthermore, many of the current therapies available have serious drawbacks; for example, polyene fungicidal agents are toxic and azole derivatives have resistance issues.² Consequently, novel therapies with low toxicity are essential for the treatment of serious fungal disease and management of topical fungal infections.

In 1993, Chu *et al.* at the Schering-Plough Research Institute reported³ the isolation of two novel quinone natural products, Sch 47554 (**1**) and Sch 47555 (**2**). These were discovered during screening processes for new antifungal agents from fermentation broths containing a strain of *Streptomyces sp.* (SCC-2136), originally isolated from a Canadian soil sample (Figure 1). Both show activity against *Candida albicans*, *C. tropicalis*, *C. stellatoidea*, *Trichophyton mentagrophytes*, *T. rubrum*, *T. tonsurans* and *Microsporum canis*, with **1** showing the greater activity. Both are complex members of the angucycline class of antibiotics, specifically members of the aquayamycin-like subclass, defined by the position and extent of oxygenation.

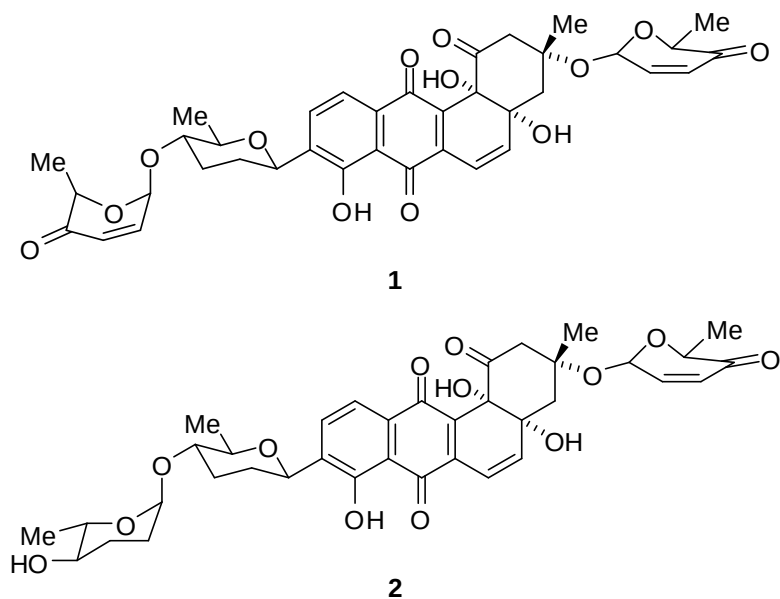


Figure 1: Sch 47554 (**1**) and Sch 47555 (**2**)

The angucycline group of antibiotics consists of more than one hundred secondary metabolites of microbial origin. They exhibit anti-tumour activity, enzyme inhibition, antiviral activity and inhibition of blood platelet aggregation.⁴ This group is defined by the angularly-fused tetracyclic ring system of the aglycone (core unit excluding any pendant sugar moieties). This tetracyclic unit is based on the benz[*a*]anthracene skeleton, **3** and is biosynthetically derived from a decaetide chain formed *via* the polyketide pathway. ‘Angucyclinone’ refers to compounds of this class without glycosidic structures attached to the tetracyclic core, and ‘angucycline’ to those which do. Representative of the angucyclinone class is tetrangomycin (**4**), the first angucycline to be discovered and of the angucycline class aquayamycin, (**5**), a more oxygenated example that was also discovered early in the history of angucyclines, which will be discussed in more detail in Section 1.2.2.

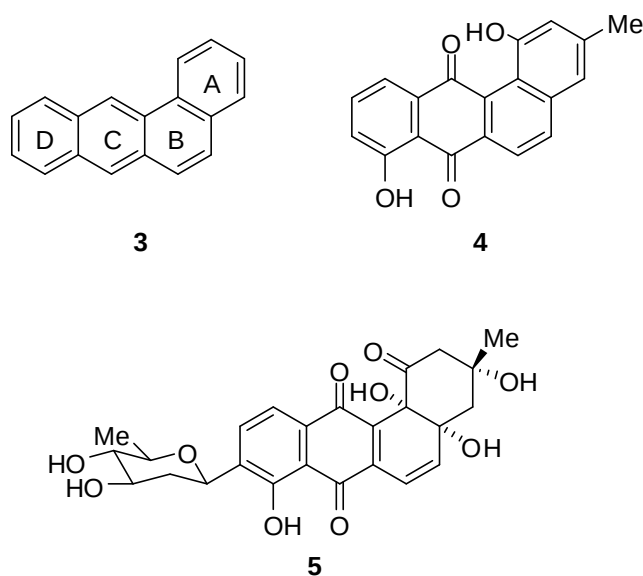


Figure 2: The Benz[*a*]anthracene Skeleton (3), Tetrangomycin (4), and Aquayamycin (5)

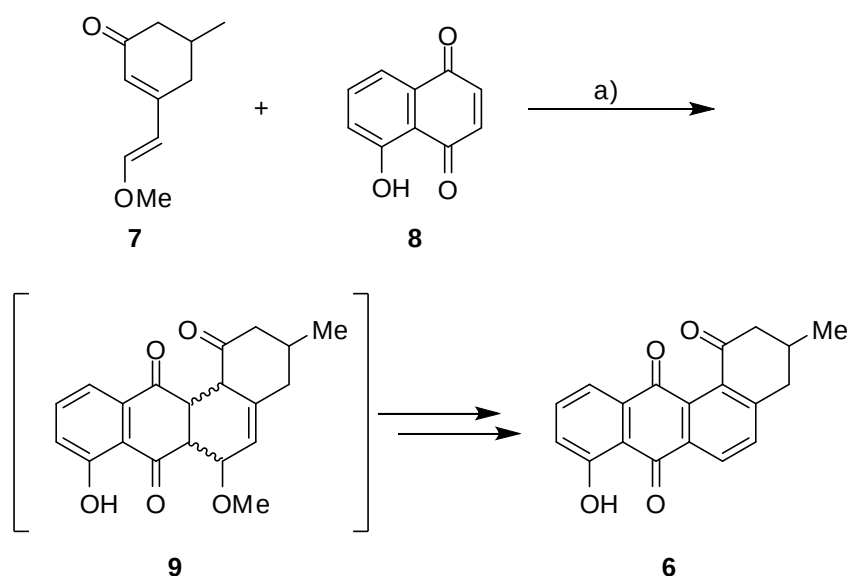
1.2 Previous studies and syntheses of angucyclines

Advances in the synthesis of angucyclines have been well documented.^{5,6} An overview of synthetic routes relevant to this project, where Diels-Alder reactions have been used to make the tetracyclic core, is presented. There are many other methods however, which are outside the scope of this overview but are reviewed elsewhere. The types of transformation successfully utilised include Friedel-Crafts acylation,⁷ Hauser annulation,⁸⁻¹⁰ other anionic annulations,^{11,12} free radical annulations,¹³ cyclobutenone rearrangements¹⁴⁻¹⁶ and cobalt-mediated [2+2+2] cycloadditions.¹⁷

1.2.1 Previous synthetic routes to angucyclines employing Diels-Alder cycloadditions

There are a variety of methods recorded to form the angucycline ring system. Among the most common is the use of the Diels-Alder reaction to form one of the rings and these syntheses will be reviewed in more detail in order to demonstrate the synthetic utility of this approach.

The strategy of coupling the DC-ring fragment with the A-ring fragment, forming the B-ring by Diels-Alder cycloaddition is a demonstrated method to arrive at the tetracyclic skeleton. The synthesis of racemic ochromycinone (**6**)¹⁸ was the first successful example of this approach, employing boron triacetate to mediate the Diels-Alder reaction between cyclohexenone **7** and juglone **8** (Scheme 1). The Diels-Alder reaction was regiochemically controlled by the methoxy group of **7** and the hydroxyl substituent of **8** interacting with the catalyst and being held in a specific orientation by these interactions so that only one regioisomer was formed.



Reagents and conditions: a) B(OAc)₃, CH₂Cl₂.

Scheme 1: The Synthetic Approach to Ochromycinone *via* a Diels-Alder Reaction

Since this pioneering work was disclosed, this strategy has been utilised in a number of syntheses,⁶ e.g. by Krohn *et al.* in the synthesis of racemic 6-deoxybrasiliquinone B (**11**),¹⁹ Larsen's syntheses of (+)-emycin A (**10**) and (+)-ochromycinone (**6**),^{20,21} and in more oxygenated species such as (+)-rubiginone A₂ (**12**) and (–)-rubiginone C₂ (**13**)²² (Figure 3).

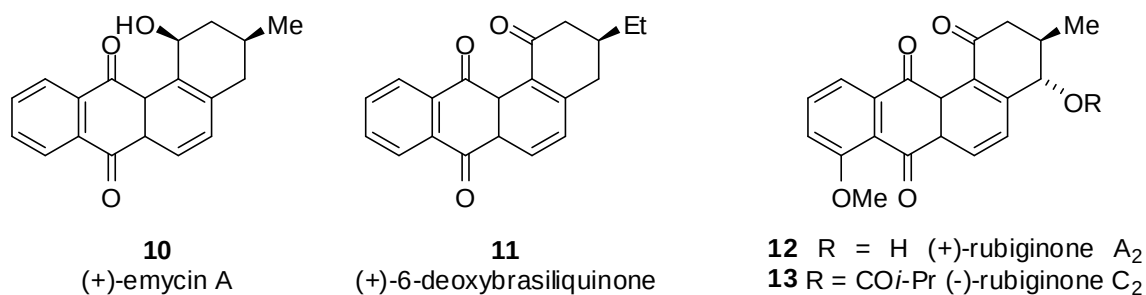
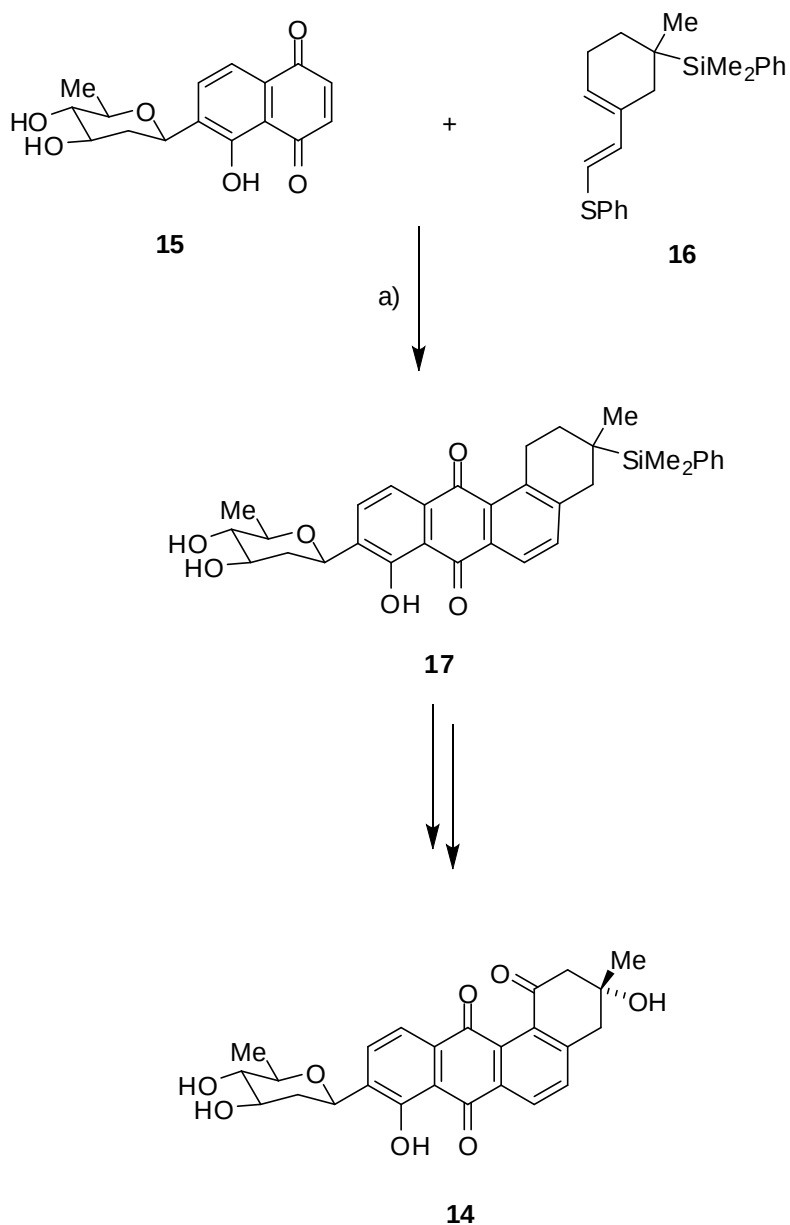


Figure 3: Some Benz[*a*]anthracene-Based Natural Products Synthesised *via* a DC + A Ring Diels-Alder Reaction

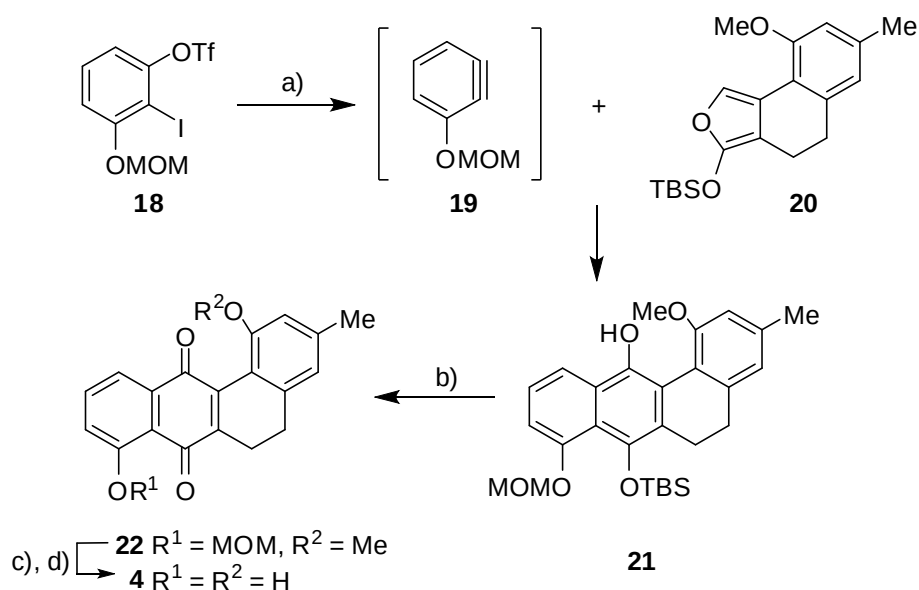
This type of strategy has also been exploited in the synthesis of C-glycosyl angucyclinones, such as Toshima's synthesis of urdamycinone B (**14**),²³ the key cycloaddition step of which is illustrated as an example of a highly regioselective cycloaddition between quinone **15** and diene **16** (Scheme 2).



Reagents and conditions: a) B(OAc)₃, CH₂Cl₂.

Scheme 2: The Diels-Alder Cycloaddition in the Synthesis of Urdamycinone B (14)

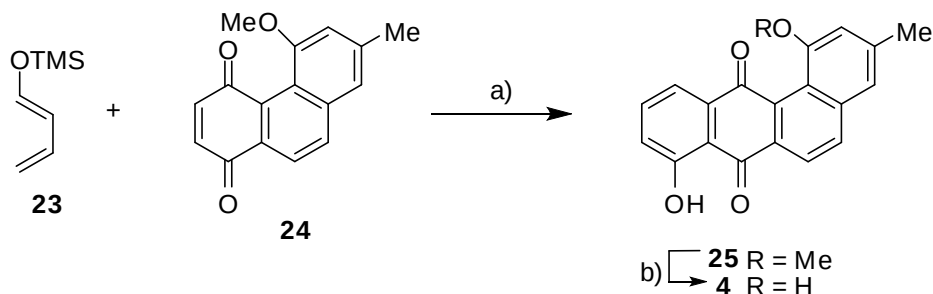
Alternative strategies exist which employ a Diels-Alder cycloaddition between a dienophile-bearing D-ring and diene-bearing BA-ring, forming the C ring in the process. This strategy has been demonstrated by Suzuki *et al.* in their synthesis of tetrangulol^{24,25} where, due to the polarisation of the benzyne and furan, excellent regioselectivity in the Diels-Alder reaction was observed (Scheme 3). **21** was formed as the major regioisomer (in a 93:7 ratio) and from this advanced intermediate the synthesis of tetrangulol (**4**) was completed.



Reagents and conditions: a) i) *n*-BuLi, -50°C , b) aq. CAN, MeCN; c) i) DBU, dioxane, Δ , 74% over two steps; d) BBr₃, CH₂Cl₂, -78°C , 100%.

Scheme 3: The Synthesis of Tetrangulol (**4**) Using a D + BA Ring Diels-Alder Cycloaddition

Another synthesis of tetrangulol was achieved with a dienophile-bearing CBA fragment + diene fragment strategy in order to form the D ring with a Diels-Alder reaction.²⁶ The key cycloaddition between 1,4-phenanthrenequinone **24** and butadiene **23** gave a single regioisomer, despite the substituents on the quinone being remote (Scheme 4). Subsequent oxidation and demethylation afforded **4**.



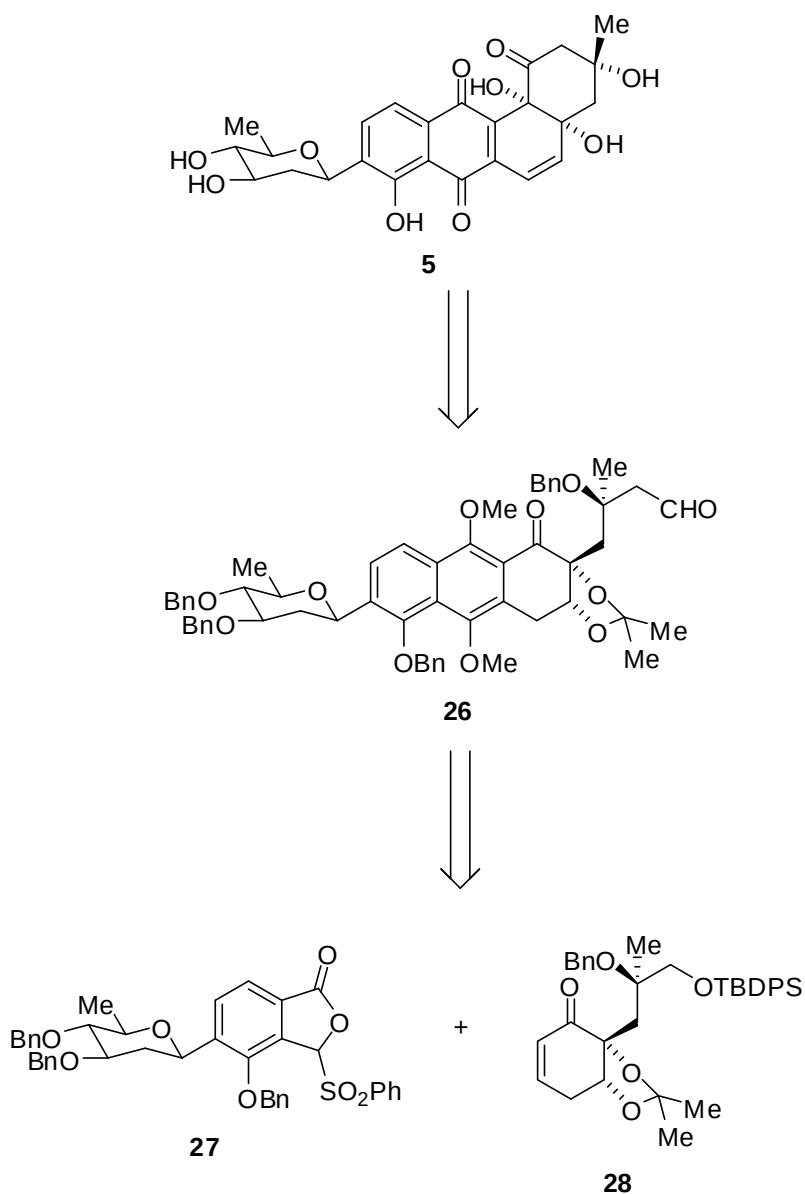
Reagents and conditions: a) i) CH₂Cl₂, rt; ii) CrO₃, H₂SO₄, 78% over 2 steps; b) TMS-I, 81%.

Scheme 4: An Alternative Synthesis of Tetrangulol, **4**, Using a CBA Dienophile + Diene Diels-Alder Reaction

These examples indicate how Diels-Alder cycloadditions are a powerful tool in the synthesis of both racemic and enantiopure angucyclines and angucyclinones and are among the most widely-used methods to achieve this. However, the syntheses of many of the more complex and polyoxygenated derivatives are still currently unachieved. With this in mind, the total synthesis of aquayamycin (**5**) is examined in greater detail, as it has a synthetically challenging polyoxygenated structure, and gives its name to the class of angucyclinone that target molecules to which Sch 47554 and Sch 47555 belong, i.e. the aquayamycin-type class,⁴ defined by a C-glycoside functionality at the aromatic carbon at C9 and the presence of two hydroxyl groups at the AB ring junction. It is amongst the most elaborate angucyclines synthesised thus far. The biological profile of aquayamycin is enhanced relative to many angucyclinones, and has been found to be a potent inhibitor of tyrosine²⁷ and dopamine²⁸ hydrolases.

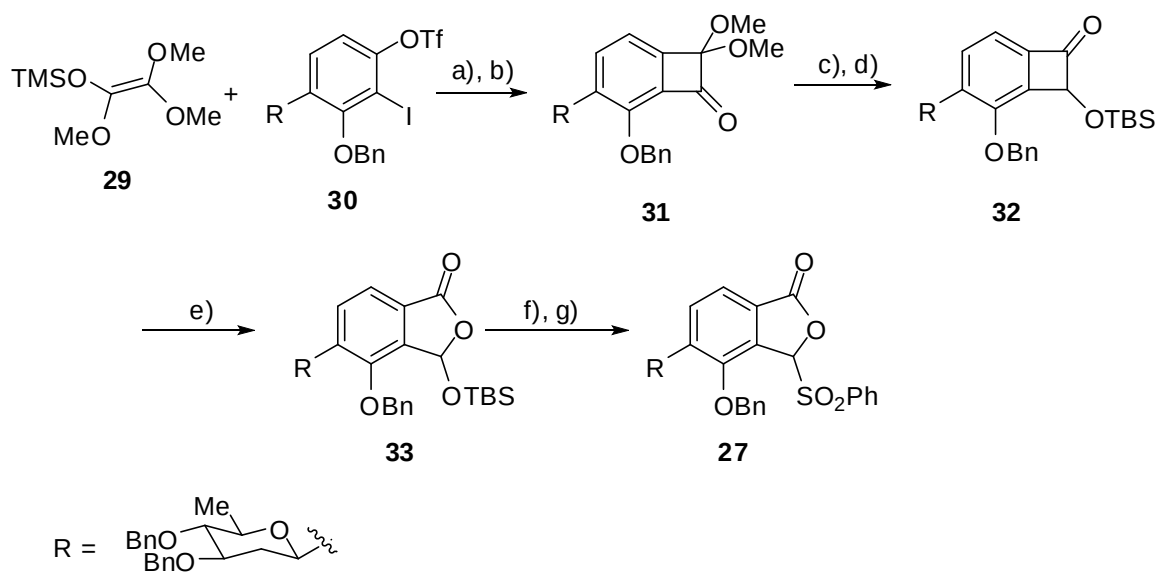
1.2.2 Total Synthesis of Aquayamycin

The first total synthesis of aquayamycin was successfully completed in 2000, by Suzuki and co-workers. Over the course of three consecutive papers, they describe their synthesis of phthalide **27**,²⁹ cyclohexenone **28**,³⁰ and the utilisation of a Hauser reaction to successfully form the C ring from the fusion of these two segments, followed by cyclisation of a pendant moiety *via* a pinacol reaction of a cycloketone-aldehyde intermediate in order to form the A ring³¹ (Scheme 5).



Scheme 5: Suzuki's Retrosynthesis of Aquayamycin (**5**)

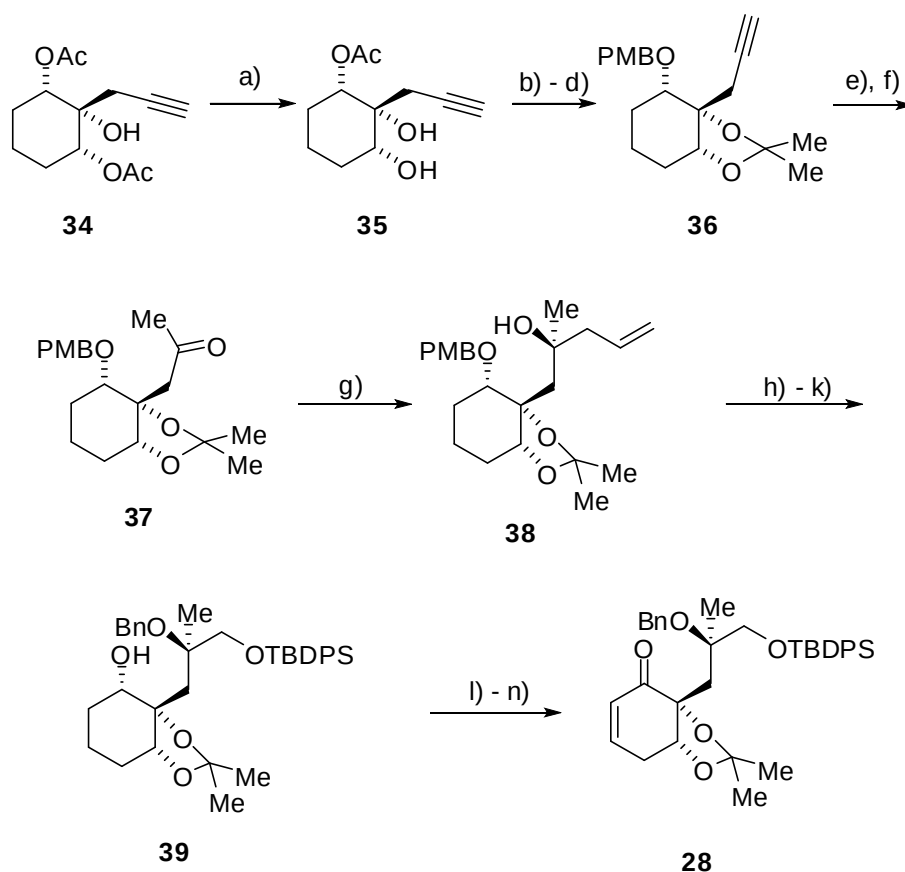
Synthesis of phthalide **27** was completed in five steps from known triflate **30**.³² Aryne formation by treatment of triflate **30** with base and [2+2] cycloaddition with the ketene silyl acetal **29** gave cycloadduct **31**, as a single regioisomer. Desilylation and hydrolysis gave ketone **32**. Baeyer-Villiger oxidation, using magnesium monoperoxyphthalate (MMPP) gave the ring-expanded product **33**. Treatment with thiophenol under acidic conditions, followed by oxidation of the sulfur centre gave the desired phthalide **27** (Scheme 6).



Reagents and conditions: a) *n*-BuLi, THF, $-78\text{ }^{\circ}\text{C}$, 20 min; b) aq. KF, (*n*-Bu)₄NCl, MeCN, 40 min, 73%, over two steps; c) i) NaBH₄, MeOH, THF, $0\text{ }^{\circ}\text{C}$, 15 min, ii) 4 M HCl, 2 h, 98%; d) TBS-Cl, imidazole, DMF, 1.5 h, 98%; e) *m*-CPBA, Na₂HPO₄, CH₂Cl₂, 88%; f) PhSH, *p*-TsOH, PhH, Δ , 1 h, 97%; g) *m*-CPBA, CH₂Cl₂, $0\text{ }^{\circ}\text{C}$, 2 h, 93%.

Scheme 6: Synthesis of Phthalide **27**

Attention was then turned to the synthesis of cyclohexenone **28** needed for the key Hauser reaction. Enzymatic hydrolysis of *meso*-acetate **34** gave optically pure diol **35** in greater than 99% ee. The vicinal diol was protected as an acetal, followed by hydrolysis of the acetate and re-protection of the revealed alcohol as a *p*-methoxybenzyl ether. The triple bond was then partially hydrogenated to the alkene, and this was subjected to Hg²⁺-mediated Wacker-type oxidation in order to obtain the correct regioselectivity in the oxidation of the olefin. Subsequent allylation with the zinc allyl species gave alcohol **38**, which was then benzyl-protected, before reductive ozonolysis of the terminal alkene yielded the primary alcohol, which was silyl-protected. The cyclic alcohol **39** was then revealed by selective deprotection of the PMB group with DDQ. Synthesis of cyclohexenone **28** was then completed by oxidation of the free alcohol and dehydrogenation of the resulting ketone *via* the enol allyl carbonate, using palladium to effect this transformation (Scheme 7).

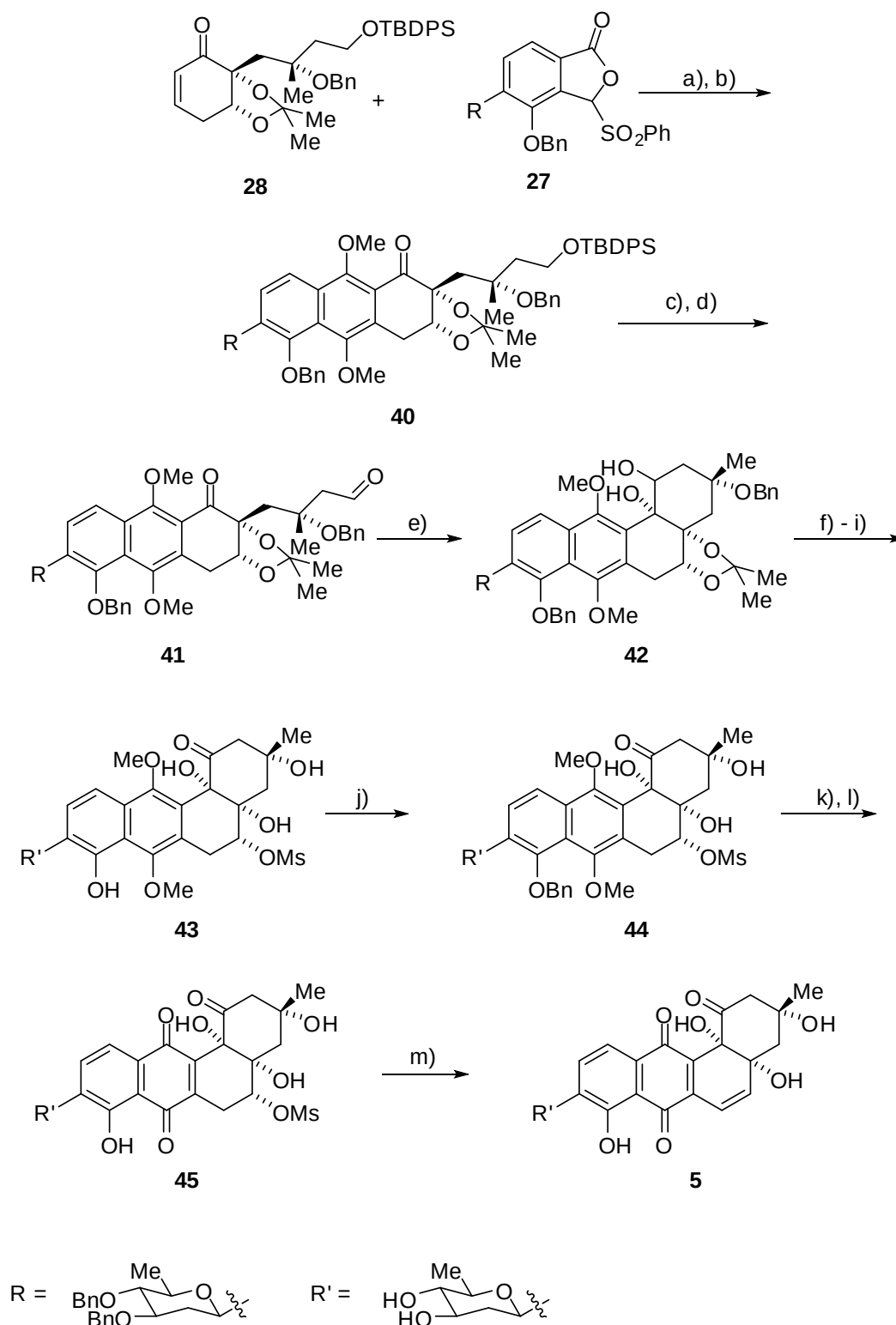


Reagents and conditions: a) *Candida Antarctica* lipase (94%, 99% ee); b) $\text{H}_2\text{C}=\text{C}(\text{OMe})\text{Me}$, TsOH, PhH, 30 min; c) K_2CO_3 , MeOH, 45 min, 97% over 2 steps; d) PMBCl, NaH, DMF, 0 °C, 2 h, 92%; e) H_2 , quinoline, Lindlar's catalyst, hexane, 70 min, 97%; f) i) $\text{Hg}(\text{OAc})_2$, MeOH, 1 h, ii) PdCl_2 , LiCl, CuCl_2 , 30 min, 80%; g) $\text{CH}_2=\text{CH}-\text{CH}_2\text{ZnBr}$, Et_2O , -78 °C, 89%; h) BnBr, KH, cat (*n*-Bu) $_4\text{NI}$, DMF, 0 °C, 1.5 h, 98%; i) i) O_3 , MeOH, -78 °C, ii) NaBH_4 , 0 °C, 1 h, 78%; j) TBDPSCl, imidazole, DMF, 25 min, 98%; k) DDQ, CH_2Cl_2 , H_2O , 0 °C, 30 min, 98%; l) $(\text{COCl})_2$, DMSO, NEt_3 , CH_2Cl_2 , -78 to 0 °C, 50 min, 94%; m) i) KHMDS, THF, -78 to -40 °C, 30 min, ii) $\text{CH}_2=\text{CHCH}_2\text{OCOCl}$, -78 °C, 100%; n) $\text{Pd}(\text{OAc})_2$, MeCN, 15 h, 82%.

Scheme 7: Synthesis of Cyclohexenone **28**

With the two fragments in hand, the Hauser annulation could now be attempted, and thence the total synthesis of aquayamycin. Using lithium *tert*-butoxide, phthalide **27** was deprotonated and subsequently annulated with cyclohexenone **28**. The resulting hydroquinone was unstable and methylated to give key intermediate **40** in 73% over two steps. Desilylation and oxidation of the hydroxyl group gave aldehyde **41**, which was subsequently utilised in an intramolecular pinacol cyclisation employing vanadium trichloride and zinc,³¹ in conjunction with the ketone functionality present. The resulting secondary alcohol in diol **42** was oxidised, before the acetal was

hydrolysed and the revealed secondary alcohol was selectively mesylated. The benzyl ethers were then hydrogenolysed, before the phenol was selectively rebenzylated using milder conditions to obtain ether **44**. The C-ring methyl ethers were oxidised to the quinone using CAN, the resulting species was then hydrogenolysed, in order to effect debenzylation, with concomitant undesired reduction to the hydroquinone. Exposure to air reoxidised the hydroquinone back to the quinone **45**, from which methanesulfonic acid was then eliminated to form the required double bond and hence complete the synthesis of aquayamycin, **5** (Scheme 7).



Reagents and conditions: a) i) $t\text{-BuOLi}$, THF, -78°C , 30 min, ii) **28**, -78°C to 45°C , 1 h; b) K_2CO_3 , $(\text{MeO})_2\text{SO}_2$, acetone, Δ , 5 h, 73% over 2 steps; c) $\text{HF}\cdot(\text{pyr})_n$, 91%; d) $(\text{COCl})_2$, DMSO, NEt_3 , CH_2Cl_2 , -78 to 0°C , 90%; e) $\text{VCl}_3(\text{thf})_3$, Zn, DMF, CH_2Cl_2 , 30 min, 89%; f) $(\text{COCl})_2$, DMSO, NEt_3 , CH_2Cl_2 , -78 to 0°C , 90%; g) 5% aq. H_2SO_4 , 1,4-dioxane, 80°C , 2 h; h) MsCl , DMAP, pyridine, CH_2Cl_2 , 1 h; i) H_2 , 10% Pd/C, EtOAc, MeOH, 9.5 h; j) BnBr , Cs_2CO_3 , DMF, 0°C , 90 min, 79% over 3 steps; k)

CAN, H₂O/MeCN, 3 min; l) i) H₂, 5% Pd/C, EtOAc ii) air; m) (*i*-Pr)₂NEt, 1,4-dioxane, 45 °C, 90 min, 58% over 3 steps.

Scheme 8: Completion of the Total Synthesis of Aquayamycin

Chapter 2: Introduction - Arynes, Their History, Generation and Synthetic Value

2.1 Historical Overview of Arynes and Evidence for Their Existence

An overview of arynes is presented here detailing the pertinent aspects of their properties, synthesis and synthetic applications, however there are numerous more comprehensive reviews published concerning all facets of the field of aryne chemistry.³³⁻⁴¹

Aryne is a general term used for any species which is formally derived from the abstraction of two hydrogen atoms from an aromatic ring; in the case of *o*-benzyne, the two hydrogen atoms are adjacent. Diradical *m*- and *p*-arynes also exist³⁴ but will not be focussed on here. The dehydrobenzene moiety, the simplest aryne, C₆H₄, is known as benzyne, and is usually represented as **46** (Figure 4). An equally valid, but rarely used, way of describing the system is **47**. The delocalisation of the aromatic π -bond is unaffected by the formation of the aryne, so the true structure of dehydrobenzene, or benzyne, is in fact most accurately represented, in a manner similar to benzene itself, i.e. between the two resonance forms. The bond formed in the generation of the aryne is localised however, as it is between two sp² hybridised orbitals orthogonal to the aromatic system at 120° and so has less-than-full overlap (**49**). It is also worth considering that the average bond order of the two species **46** and **47** is 2.5, not 3 (assuming the mesomers are of equal probability) so the term “aryne” with -yne implying a triple bond is, although popular due to the prevalence of **46** in depicting benzyne, not completely accurate.

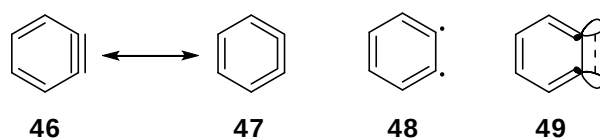
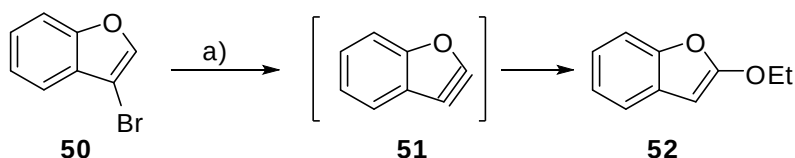


Figure 4: Various Depictions of Benzyne

The first suggestion of the existence of arynes with any evidence was made over 100 years ago, when Stoermer and Kahlert⁴² allowed benzofuran **50** to react with base in ethanol and obtained benzofuran **52** as a product (Scheme 9). They postulated the intermediate 2,3-didehydrobenzofuran (**51**).



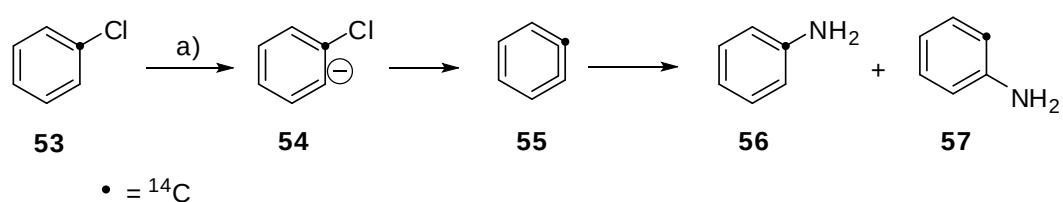
Reagents and conditions: a) base, ethanol.

Scheme 9: First Evidence for Formation of an Aryne Species, **51**

Reactions involving the dehydrobenzene intermediate had been known before then, however. The formation of biphenyl from bromobenzene and sodium was reported⁴³ in 1864 and for this reaction it was later determined that an aryne intermediate was present. It was not however suggested in any mechanism, despite that at that time the concept of such a strained intermediate would have been rather less of a problem than at the time when it was eventually proven. Other accurate speculation of an aryne as an intermediate in reaction mechanisms after **51** include in the aryl-phenol rearrangement,⁴⁴ the interaction of amylsodium with chlorobenzene⁴⁵ and as an intermediate in the reaction between phenyllithium and fluorobenzene.⁴⁶

The strongest and most decisive piece of evidence for the existence of arynes then came from Roberts *et al.*^{47,48} who allowed ¹⁴C-labelled chlorobenzene (as well as, separately, ¹⁴C-labelled iodobenzene) to react with potassium amide in liquid ammonia (Scheme 10), and determined the product distribution. If benzyne was an intermediate, ammonia could attack either end of the symmetrical strained bond, which would give rise to a 1:1 ratio of *ipso*- and *cine*-substituted products, **56** and **57** respectively. The result of the experiment gave an almost 1:1 ratio of anilines (52:48 in favour of the *cine*-substituted product was the exact ratio, which can be accounted for by the kinetic isotope effect present when attacking a ¹⁴C centre versus a ¹²C centre; it is marginally more favourable to attack ¹²C and hence form the *cine*-substituted product) which gave a very strong indication of the benzyne intermediate. Other ²H kinetic isotope effect studies were undertaken by Roberts *et al.*⁴⁹ to prove

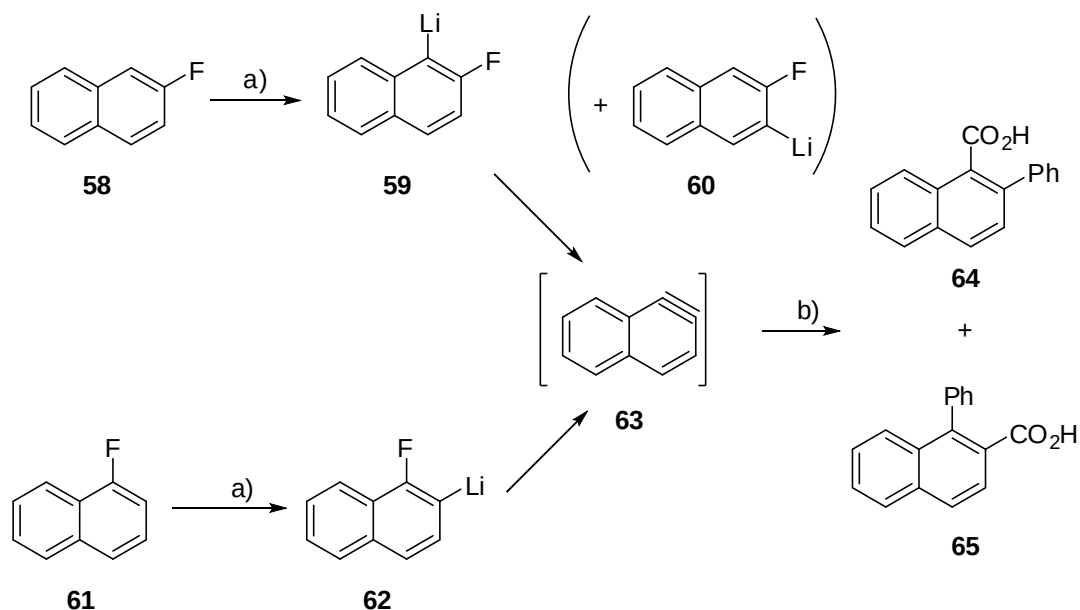
that the deprotonation of the halobenzene was the rate-determining step and thus proving other potential mechanisms (such as addition-substitution-elimination) unlikely, as they would require aromatisation to be the slow step, and the endothermic addition of ammonia across an aromatic system to be a rapid equilibrium. These studies certainly proved that the mechanism followed a path in which the two positions became equivalent and it was also demonstrated that by far the most plausible of these is *via* an aryne.



Reagents and conditions: a) KNH_2 , NH_3 .

Scheme 10: The Reaction of ${}^{14}\text{C}$ -Labelled Chlorobenzene and Potassamide *via* a Benzyne Intermediate

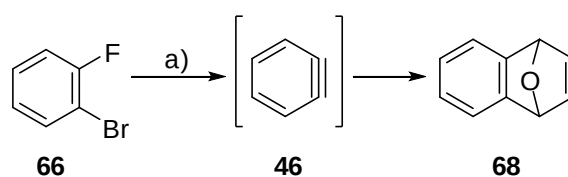
Further proof of this symmetrical intermediate came with Husigen's work on fluoronaphthalenes.^{50,51} Here, reaction of 1- and 2-fluoronaphthalene with phenyllithium and subsequent carboxylation gave exactly the same ratio of 1-phenyl-2-naphthoic acid to 2-phenyl-1-naphthoic acid (1:2), indicating a common intermediate, naphthyne **63** (Scheme 11). In the case of 2-fluoronaphthalene, the formation of another aryne, resulting from elimination of lithium fluoride from aryllithium **60** is possible as well, giving other acids.



Reagents and conditions: a) PhLi; b) CO₂.

Scheme 11: The Reaction of Phenyllithium with Fluoronaphthalenes

Another important transformation in the history of aryne chemistry was the trapping of the intermediate **46** with furan in a Diels-Alder cycloaddition by Wittig *et al.*⁵² which is still amongst the most synthetically useful reaction of arynes, as well as being an important piece of evidence for their existence. Although not a true triple bond, in this reaction the aryne **46** acts as an alkyne-type dienophile, with the resulting cycloadduct **68** indicating the species reacts as though containing a formal triple bond (Scheme 12).



Reagents and conditions: a) Li amalgam, furan.

Scheme 12: First Trapping of an Aryne with a Diene

In 1963, the pyrolysis of diiodobenzenes was examined, and mass spectrometry identified *ortho*-benzyne, on the basis of the measured ionisation potential.⁵³ Around the same time, Berry *et al.* characterised *ortho*-benzyne as a product of photoinitiated

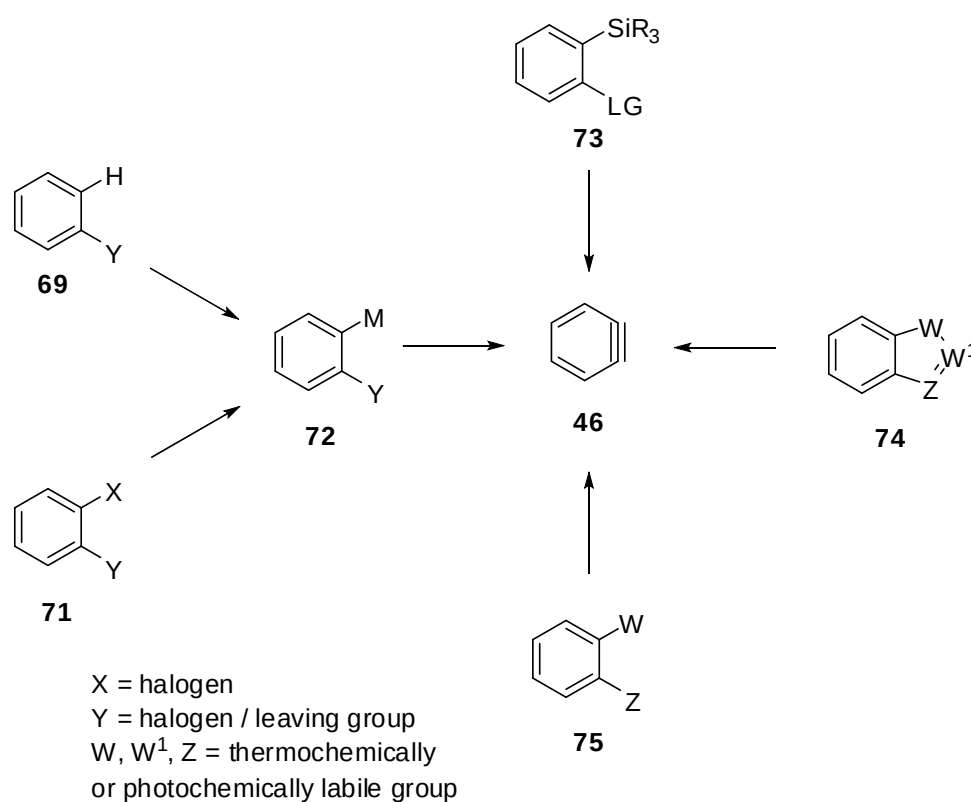
decomposition of benzenediazonium carboxylates in the gas phase, using mass spectrometry and UV spectroscopy.^{54,55} The first direct evidence for the intermediacy of arynes came from Chapman *et al.* in 1973⁵⁶ using very low temperature matrix isolation spectroscopy to photochemically generate *ortho*-benzyne from phthaloyl peroxide or benzocyclobutenedione and using IR spectroscopy to identify the products. Unfortunately, the initial assignment was found to be incorrect; the “benzyne” peak at 2045 cm⁻¹ was actually due to an alternative ketene-containing product. Later in 1992, Radziszewski *et al.*⁵⁷ assigned and proved the C≡C type bond stretching vibration was at 1846 cm⁻¹. This bond is certainly a lot weaker than a strain-free alkyne, where the C≡C stretching vibration is of the order of 2150 cm⁻¹. Then, in an elegant piece of work from 1997, Warmuth managed to isolate *ortho*-benzyne inside a hemicarcerand, by irradiating benzocyclobutenedione.⁵⁸ This isolation enabled detailed NMR analysis of the benzyne for the first time.

Current analysis still has no definitive description of benzyne, as there is still very little direct evidence of the benzyne moiety. However, the favoured description is that of a strained alkyne, rather than a biradical or a cumulene. The carbon atoms concerned maintain sp² hybridisation and the two singly-filled orbitals, in the plane of the ring, overlap, albeit poorly. A biradical species is unfavoured because of the large singlet-triplet splitting⁵⁹ of around 37.5 kcal.mol⁻¹. Although the coupling constant data from the NMR studies of Warmuth suggested that the benzyne structure exhibits a strong amount of cumulenenic character and exists considerably as mesomer **47**, this is contradicted by the most recent *ab initio* calculations⁶⁰ which suggest that the in-plane π-bond induces a small amount of bond localisation resulting in more acetylenic character. Although the low frequency of the IR stretch suggests a substantial loss of alkyne character from that of a true triple bond, the acetylenic character is also supported by alkyne-like reactivity in cycloaddition reactions, e.g. in Diels-Alder reactions with dienes.

2.2 Formation of Arynes

2.2.1 General Concepts

Arynes are too reactive to be successfully stored, and must be generated *in situ*. There are many types of precursor, requiring different conditions to form the aryne, and the choice of which to use is influenced by the ease of synthesis of the starting material, the conditions required for reaction of the aryne, consideration of other functionalities in the system and the nature of the subsequent chemistry.



Scheme 13: Different Methods Employed for the Synthesis of Arynes

There are four major classes of reaction, which are summarised in Scheme 13. The original method that was used by many of the researchers who elucidated the benzyne mechanism is direct deprotonation of a haloarene. Halides (F and Cl) increase the acidity of the proton(s) in the *ortho*-position, and consequently the protons can be

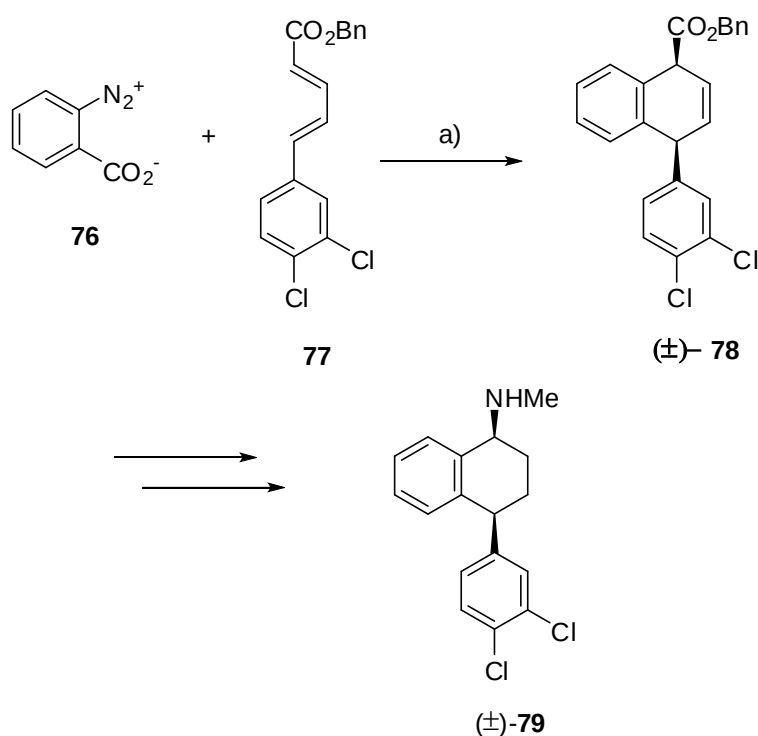
removed by a variety of strong bases at low temperature to give the metallated species **72**.

Similarly, use of halogen-metal exchange (Br and I) on a halogen centre *ortho* to a leaving group (often another halogen or pseudohalogen) results in a metallated species *ortho* to a leaving group, **72**, which can then eliminate to form the aryne. The thermodynamic driving force of this method is the breaking of the carbon-metal bond and the transfer of negative charge from an sp^2 carbon to the leaving group, which is much more able to stabilise a negative charge.

The third method is to use an arylsilicon species *ortho*-substituted with a leaving group of the type **73**. One of the most popular methods of aryne generation in recent times is the fluoride-mediated desilylation of an *ortho*-trimethylsilyl aryl triflate⁶¹ (Scheme 13, **73**, $SiR_3 = SiMe_3$ and LG = OTf). Hypervalent iodine species can also be used as the leaving group⁶² (Scheme 12, **73** $SiR_3 = SiMe_3$, LG = IPhOTf). These methods are driven by strong Si-F bond formation and generally have the advantage of needing milder conditions in order to generate the aryne and so are compatible with a wider range of functionalities. The disadvantages are the incompatibility with silyl protecting groups or other silicon centres within the molecule and that the precursor can sometimes be difficult to synthesise in more complicated species.

The final two methods in Scheme 13 are both related to the obtaining of arynes through thermal, chemical or photochemical decomposition of benzofused heterocycles or other thermally unstable systems, where the aryne is formed with the evolution of small, stable, usually gaseous molecules, such as N_2 , CO or CO_2 . An example of the use of a benzofused system is the thermal (or lead tetraacetate-mediated) decomposition of 1-aminobenzotriazoles (**74**, $W = W^1 = N$, $Z = N-NH_2$).⁶³ The latter type of system is typically the thermal decomposition of the carboxylate-diazonium zwitterions⁶⁴ (Scheme 13, **75**, where $W = CO_2^-$ and $Z = N_2^+$), which has the advantage of not requiring any reagents to generate the aryne. The major disadvantages of this method are the explosive nature of the precursor and the high temperatures required to generate the aryne. An example of a synthetic application of this precursor⁶⁵ is shown in Scheme 14. The diazocarboxylate **76** and diene **77** were

heated at 60 °C to generate the dihydronaphthalene **78** which was subsequently converted into the target molecule.



Reagents and conditions: a) DCE, 60 °C

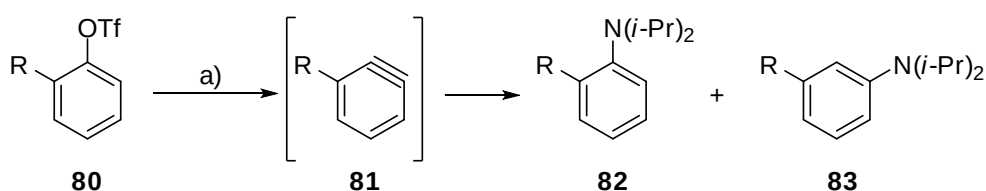
Scheme 14: The Benzyne-Diene Cycloaddition in the Synthesis of (±)-Sertaline (**79**)

The remainder of this section will discuss only the first two methods; deprotonation of a haloarene, and halogen-metal exchange of an *ortho*-halo substituted compound, as this is the method of generation that will be most relevant to this project.

2.2.2 Formation of Arynes: Deprotonation of Aryl Halides

As is evident from the examples of Roberts *et al.* and Wittig *et al.*,^{46-48,52} aryl halides can be deprotonated by strong bases *ortho* to the halogen. This is valid for all halogens except for iodine, although in the case of bromine, metal-halogen exchange is a competitive process. In the previous example of Roberts, where liquid ammonia was used as the solvent, the benzyne thus formed was quenched by ammonia and forms a pair of isomeric anilines in a 1:1 ratio. Etheral solvents can also be used, which extends the range of reactions available to the benzyne.³⁸

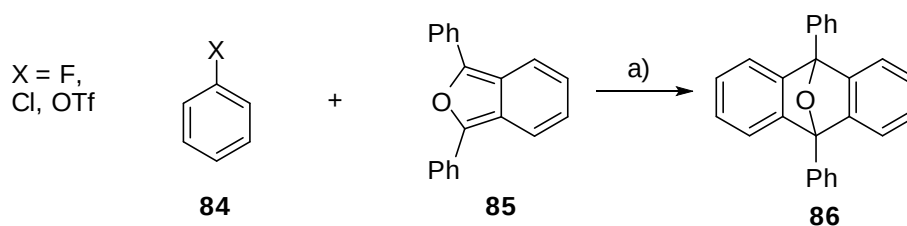
Pseudohalides can also be subjected to this procedure. Aryl triflates can be deprotonated by lithium di-*iso*-propylamide, which eliminates lithium triflate and forms the aryne **81**, which is subsequently quenched by the amine present, to give the substituted anilines **82** and **83** (Scheme 15).⁶⁶ This pair of *ortho*-isomers and *cine*-substitution is indicative of aryne formation. The use of benzenesulfonates as aryne precursors was also examined, but the poor yields mean that they are not widely used under deprotonative conditions.⁶⁷



Reagents and conditions: a) *n*-BuLi, *i*-Pr₂NH, -78 °C.

Scheme 15: Aryne Formation from Aryl Triflates

Deprotonation of an aryl halide or triflate with a zincate, with subsequent aryne formation, has also been reported, with subsequent Diels-Alder cycloaddition reaction between the aryne and a substituted furan to give the relevant cycloadduct **86** in very high yield (Scheme 16).⁶⁸



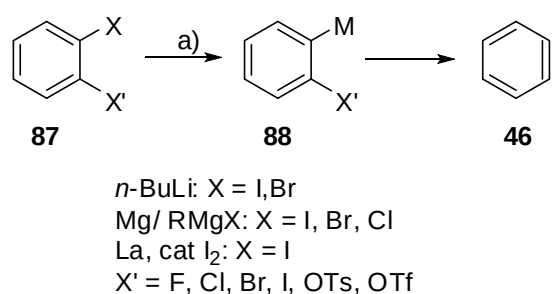
Reagents and conditions: a) Me₂Zn(TMP)Li, THF, Δ, 12 h, 99%.

Scheme 16: Use of Lithium Dimethyltetramethylpiperidinozincate in Aryne Formation

2.2.3 Formation of Arynes: Halogen-Metal Exchange

Previously described methods for aryne generation relied on deprotonation of an aromatic ring, and even with the electron-withdrawing effect of the halogen, this

requires very strong bases, which can be incompatible with other functionalities. In addition, there can sometimes be more than one sufficiently acidic proton and this can lead to regioisomers being formed. The use of *ortho*-dihaloarenes avoids these potential problems, as these species can be treated with a metallic species (lithium,⁶⁹ *n*-butyllithium,⁷⁰ magnesium⁷¹ or lanthanum with catalytic iodine^{72,73}) and then eliminate to give the desired aryne (Scheme 17). As above, it is not just halogens which can act as good leaving groups, aryl *ortho*-halotosylates^{74,75} and *ortho*-halotriflates⁷⁶ are also used in these halogen-metal exchange reactions. In addition, a wide range of *ortho*-iodo aryl sulfonates have been reacted with *iso*-propylmagnesium chloride to form the aryne intermediate,⁷⁷ a method which is mild and tolerant of a wide range of functionalities.



Reagents and conditions: a) *n*-BuLi, – 78 °C or RMgX or Mg, Δ or La, cat. I₂.

Scheme 17: Aryne Generation Methods Using Halogen-Metal Exchange

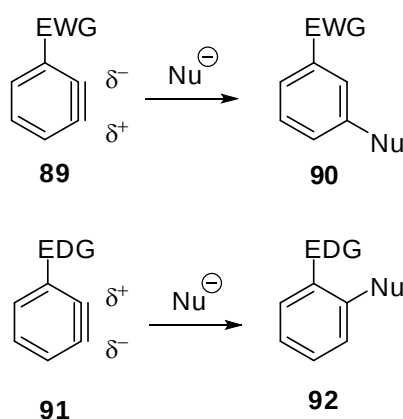
2.3 Reactions of Arynes

The defining feature of the aryne is the partial triple bond which is highly strained and electrophilic. Because of this, there are two main categories of reaction which dominate the reactivity of arynes; cycloadditions and nucleophilic additions.

2.3.1 Nucleophilic Addition to Arynes

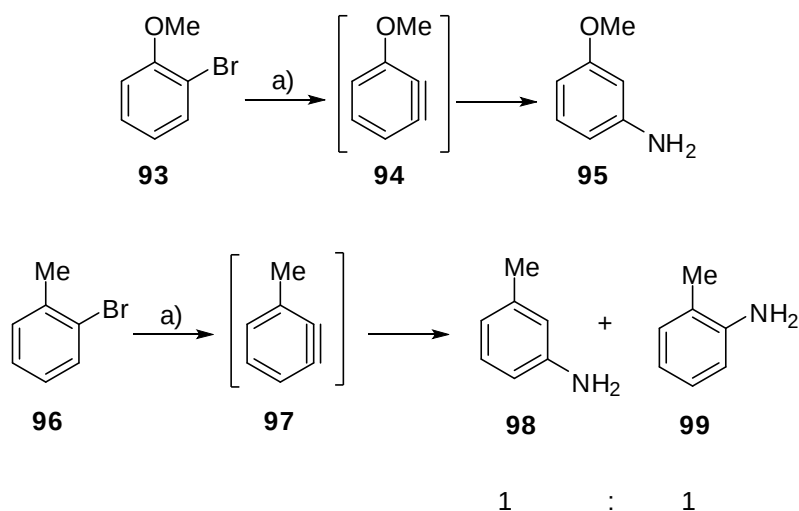
Although a very important and useful area of reactivity of arynes, nucleophilic addition to arynes is less relevant to the project and so will only be briefly examined. Arynes are, in principle, electrophilic at both ends of the triple bond and due to their extreme electrophilicity, good selectivity can be more of an issue than for many other

electrophiles, though in some cases it is evident, especially at low temperature.⁴⁰ The regioselectivity of addition is influenced by the nature of the substituents on the aryne ring. Inductively electron-withdrawing groups (EWGs) will polarise the aryne bond as shown (Scheme 18), favouring *meta*-addition of the nucleophile, whereas inductively electron-donating groups (EDGs) will polarise the bond in the opposite sense, favouring *ortho*-addition. This is due to the inductive effect of the substituents transmitted through the σ -framework only, and not with any π -conjugated resonance stabilisation (which would polarise the bond in the reverse sense). This is because the relevant p-orbitals forming the weak π -bond of the aryne (the HOMO) are orthogonal to the other p-orbitals involved in delocalisation and thus does not participate in, or is affected by, the π -system present in aromatic molecules.



Scheme 18: Polarisation of the Electrophilic Partially-Triple Bond in Arynes

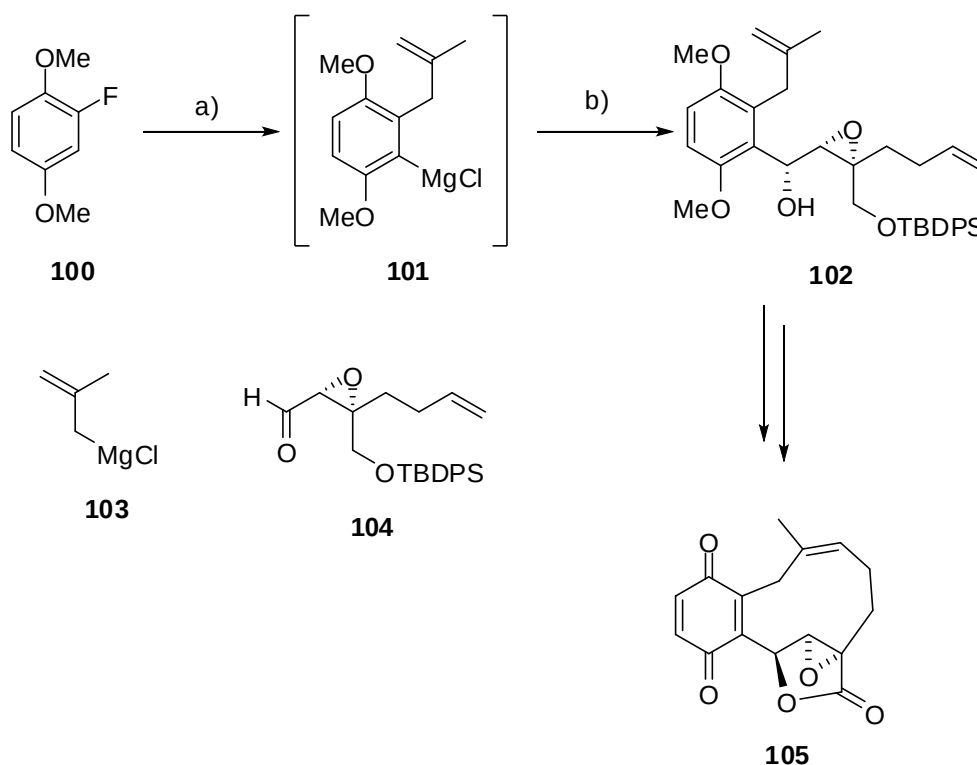
This selectivity is demonstrated even in Roberts's early mechanistic work⁴⁸ (Scheme 19). The methoxy group is strongly inductively electron withdrawing, directing the nucleophile to the *meta*-position when attacking aryne **94** to give exclusively **95**. However, the much weaker induction from the methyl group produces a mixture of regioisomers (**98** and **99**) that is close to 1:1, and therefore does not polarise the bond and the nucleophile is not directed and reacts indiscriminately.⁷⁸



Reagents and conditions: a) NaNH₂, NH₃, (l)

Scheme 19: Addition of Ammonia to Differently Polarised Benzyne

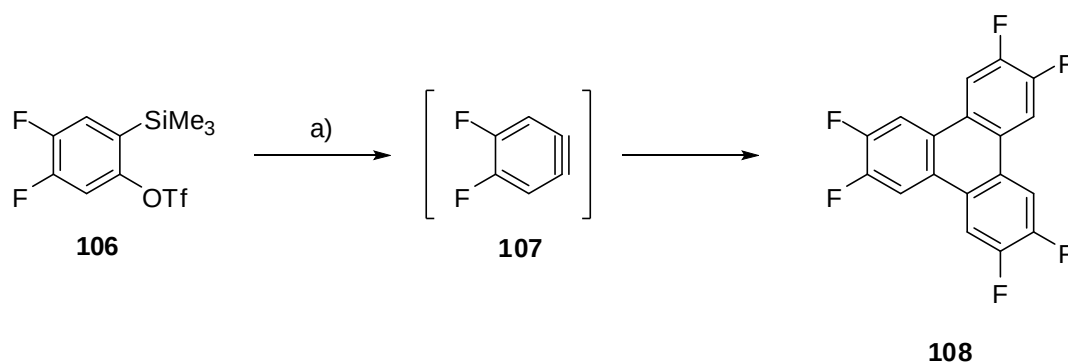
A variety of nucleophiles have been added to arynes, reviews of which are numerous and comprehensive.^{37,38,41} An example from a previous synthesis within the research group demonstrates that the introduction of two adjacent carbon chains onto an aromatic cycle is possible, with a reasonable yield, whereby the organomagnesium species attacks the aryne generated from fluoride **100** and the resulting carbocation **101** is quenched by an aldehyde to give the benzylic alcohol **102** (Scheme 20). This reaction was the key building block in this synthesis of *ent*-clavilactone B (**105**).⁷⁹



Reagents and conditions: a) i) *n*-BuLi, $-78\text{ }^{\circ}\text{C}$, **103**, ii) $-78\text{ }^{\circ}\text{C}$ to rt; b) **104**, 65%

Scheme 20: The Introduction of Two Adjacent Carbon Chains to an Aromatic Ring via Magnesiated Species **101**

Transition metal-catalysed reactions of arynes is a relatively new field of chemistry and is finding application in areas of synthetic value, such as the trimerisation of arynes, an example of which is shown in Scheme 21.⁸⁰ The aryne is generated from the *ortho*-silylphenyl triflate and fluoride and the resulting aryne trimerises due to the presence of the palladium, as without it no trimer is detected. Since this result, more examples have been carried out and aryne trimerisation has been recently reviewed.⁴¹



Reagents and conditions: a) 0.1 eq. $[\text{Pd}(\text{PPh}_3)_4]$, CsF, MeCN, rt, 52%.

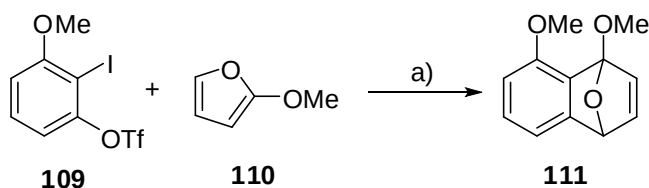
Scheme 21: The Trimerisation of Arynes

2.3.2 Cycloaddition Reactions of Arynes

This category of reactions is potentially the most important that arynes can undergo, due to the significant increase in complexity this transformation affords. The most important of these reactions is the [4+2] Diels-Alder cycloaddition, but arynes will undergo [2+2] cycloadditions as well (e.g. in their own dimerisation), and can partake in 1,3-dipolar cycloadditions and the ene reaction. All types of aryne cycloaddition reactions have been comprehensively reviewed.^{33,36-41}

Arynes, being highly electrophilic and of pseudo-triple bond character, react with a wide range of dienes. Because of their short-lived nature, resulting from their indiscriminate reactivity, the cycloaddition proceeds more successfully with dienes which are permanently, or readily available, in the cisoid conformation, and thus closest to the transition state for good orbital overlap with the partial triple bond of the aryne. Therefore, five-membered aromatic heterocycles are particularly good dienes, but many dienes are suitable, and the electrophilicity of arynes is such that they can even undergo cycloaddition to benzene.³⁵ It is however, worth noting that, because of the exceptional electrophilicity of the aryne, competing reactions such as the [2+2] cycloaddition and the ene reaction are significant side reactions more frequently than for less reactive dienophiles, particularly if the diene is not conformationally favourable for the [4+2] cycloaddition.

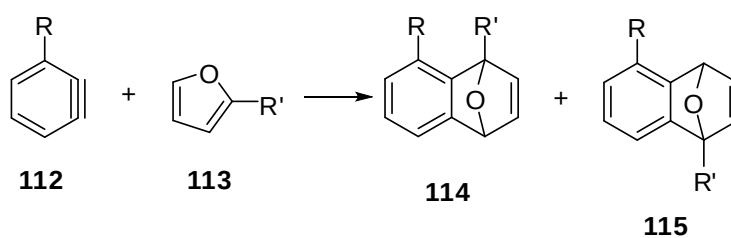
Similarly to nucleophilic addition, regioselectivity in the Diels-Alder reaction can be observed if both the diene and aryne have substituents. Only the inductive effect polarises the benzyne as before, but the diene, of which the electrons of the delocalised π -system are used in the reaction, is influenced by the resonance forms available. An illustrative reaction is that between the aryne derived from **109** and furan **110**, which gives exclusively *syn*-isomer **111**, coined the “head-to-head” product by Suzuki *et al.*⁷⁶



Reagents and conditions: a) *n*-BuLi, THF, – 78 °C, 10 min.

Scheme 22: The Regioselective Cycloaddition of Substituted Aryl Triflate **109** to Furan **110**

Regioselectivity of cycloadditions can also be affected by steric factors. The methoxy (OCH₃) and the methoxycarbonyl (CO₂Me) are almost identical in their inductive effect (σ_1 values of 0.27 and 0.30 respectively).⁸¹ Therefore, in the cycloaddition reactions of a 2-substituted furan with 3-methoxybenzyne (R = OMe) and 3-(methoxycarbonyl)benzyne (R = CO₂Me), the ratio of *syn:anti* products should be similar, if inductive electronic effects were the only factor. However, Sargent *et al.*⁷⁵ demonstrated that there is a large variation in the ratio of *syn:anti* products observed, with the ratio consistently biased towards *anti* cycloadducts for products arising from 3-(methoxycarbonyl)benzyne. This indicates that the steric bulk of the ester group, even when allowed to react with the modestly-sized 2-methylfuran, is enough to overcome the electronic induction, and steric effects begin to dominate the regioselectivity of the reaction (Scheme 23).



Scheme 23: The Cycloaddition Reaction Between Benzyne **112** and 2-Substituted Furans **113**

Entry	R' =	<i>syn:anti</i> Ratio for R =	<i>syn:anti</i> Ratio for R =
		OMe	CO ₂ Me
1	Me	70:30	43:57
2	<i>i</i> -Pr	74:26	30:70
3	<i>t</i> -Bu	85:15	23:77
4	OAc	75:25	38:62
5	Br	63:37	17:83
6	CO ₂ Me	56:44	33:67

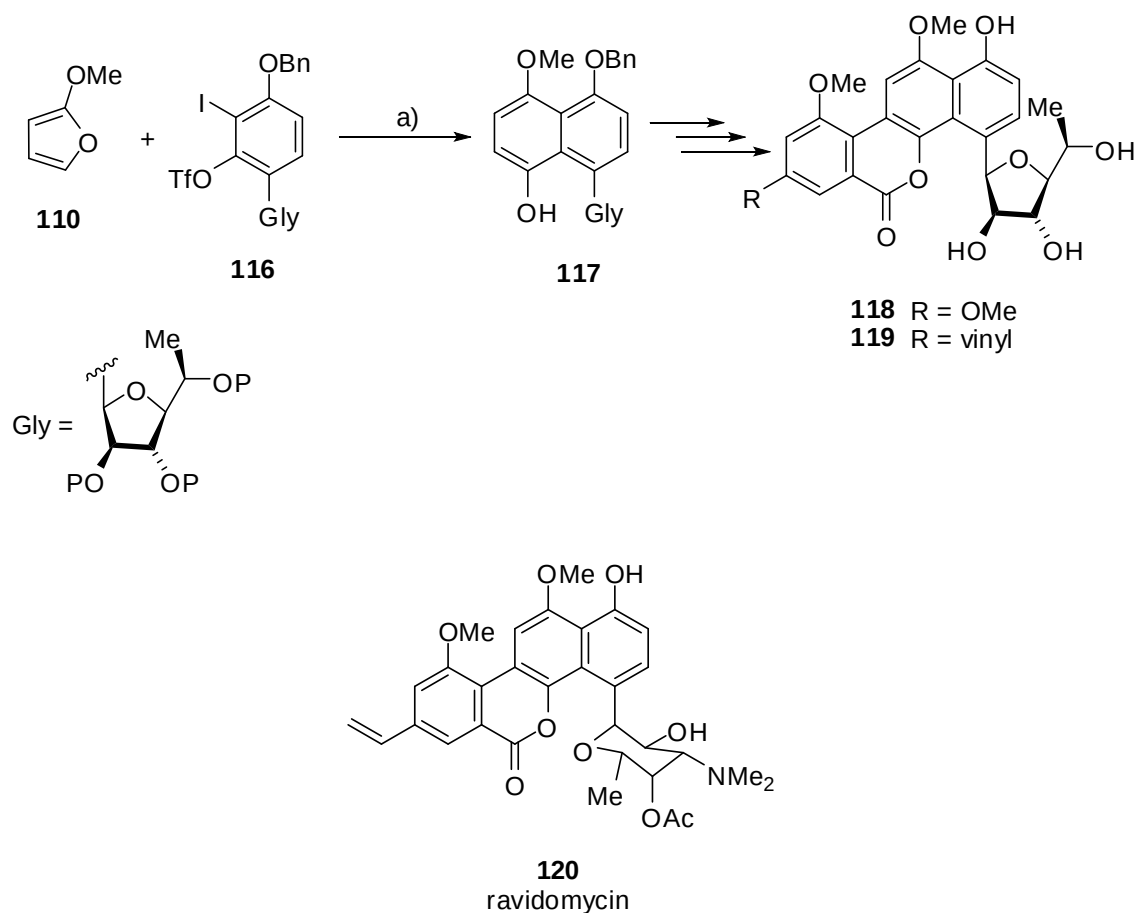
Table 1: The Ratios of the Isomers Resulting From the Cycloaddition in Scheme 23

2.3.3 Aryne-Furan Diels-Alder Reactions in Synthesis

The Diels-Alder reaction between an aryne and a furan is one of the most common uses of the aryne intermediate. As described above, furan is a particularly good diene in these reactions, and moreover, the resulting oxabenzonorbadiene motif is a useful and versatile synthetic intermediate, e.g. acid-catalysed cleavage of the oxygen bridge results in aromatisation and formation of a naphthol. There is also an alkene functionality separate from the aromatic section, of which all usual alkene chemistry is possible. The following examples of aryne-furan cycloaddition in synthesis demonstrate the value of this transformation.

In the elegant synthesis of the gilvocarcins by Suzuki *et al.*,⁸² a benzyne-furan cycloaddition reaction is one of the key steps to build the naphthalene moiety **95** (Scheme 21). The reaction utilised a sugar-bearing methoxybenzyne species and 2-methoxyfuran, and gave the regioselectivity previously observed, i.e. the *syn* (or head-to-head) product as the major (93:7) isomer. The high yield of the cycloaddition reaction and the excellent regioselectivity, make this a very impressive result, and particularly relevant to utilisation of aryne-furan reactions in the synthesis of angucyclinone-type structures. This can then be transformed into gilvocarcin M (**118**)

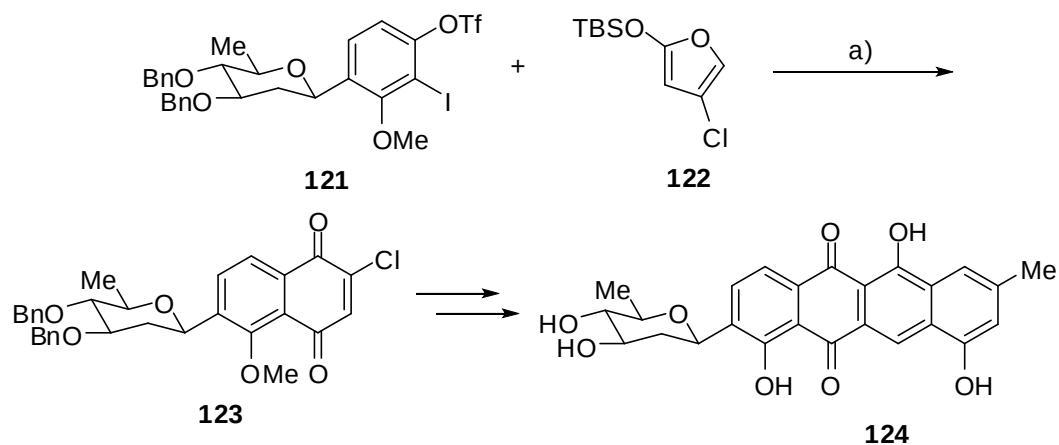
or gilvocarcin V (**119**). Similar methodology was also used to complete the synthesis of ravidomycin (**120**), an amino-sugar variant of the gilvocarcin antibiotics.



Reagents and conditions: a) *n*-BuLi, THF, -78°C , 10 minutes, 88%.

Scheme 24: The Aryne-Furan Reaction in Suzuki's Synthesis of the Gilvocarcins

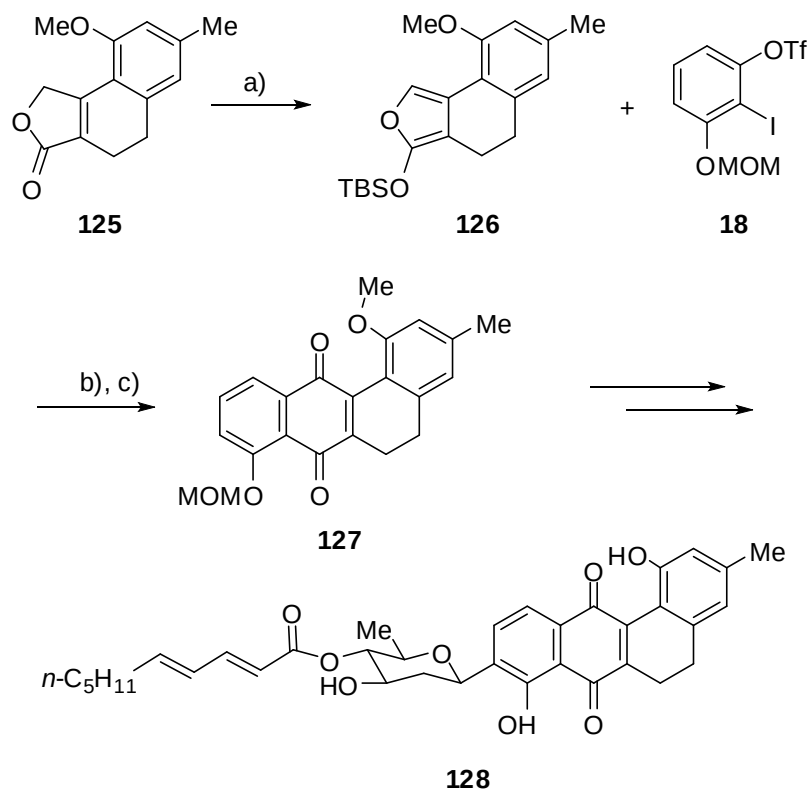
Further applicability was demonstrated by Suzuki *et al.* for other classes of antibiotics, namely in the total synthesis of galtamycinone (**124**), and a new route to the general aglycon of *C*-glycosyl naphthacenequinone antibiotics.⁸³ Regioselective aryne-furan cycloaddition between the benzyne derived from iodotriflate **121** and furan **122** gave juglone **123**, after spontaneous aromatisation of the cycloadduct and oxidation using ceric ammonium nitrate in excellent yield.



Reagents and conditions: a) i) *n*-BuLi, THF, $-78\text{ }^{\circ}\text{C}$; ii) aq. CAN, MeCN, $0\text{ }^{\circ}\text{C}$, 91%.

Scheme 25: The Aryne-Furan Cycloaddition in the Synthesis of Galtamycinone (**124**)

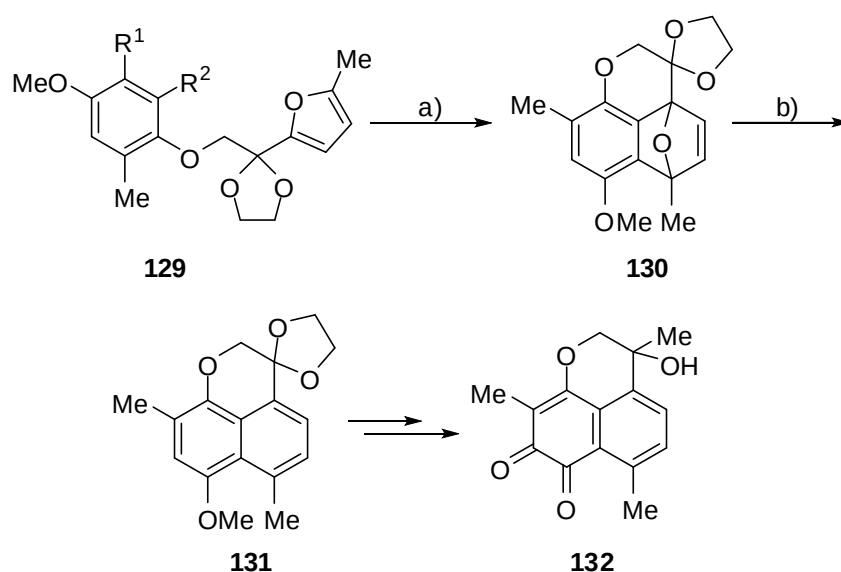
A further application of this methodology by Suzuki *et al.* was demonstrated in the total synthesis of the antibiotic C104 (**103**).^{84,85} The cycloaddition between the aryne derived from iodotriflate **106** and furan **105** was again regioselective for the *syn* product (14:1). The cycloadduct from the aryne-furan cycloaddition was unstable and spontaneously aromatised, and even the naphthol product was not isolated, but immediately oxidised (CAN) to the quinone **107** in good yield (Scheme 26).



Reagents and conditions: a) NaH, TBSCl, THF, 50 °C; b) *n*-BuLi, THF, –50 °C; c) aq. CAN, MeCN, –10 °C, 76% over 3 steps

Scheme 26: The Aryne-Furan Cycloaddition in the Synthesis of the Antibiotic C104 (128)

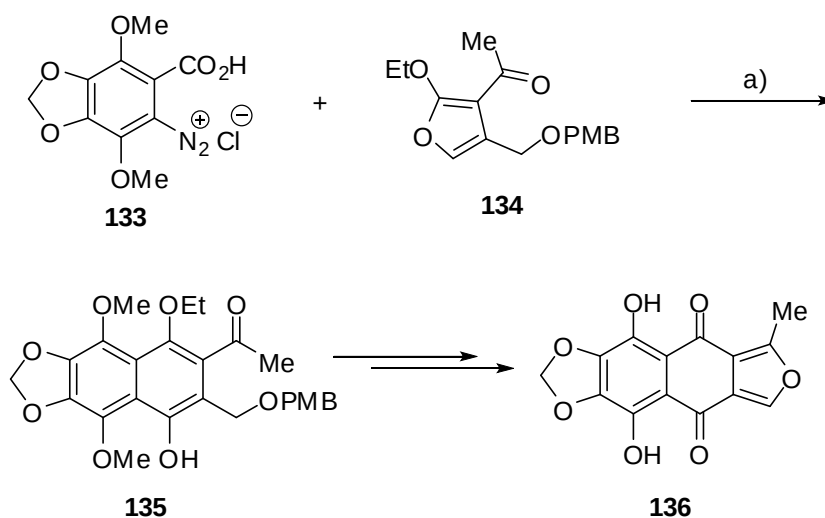
An example where a key transformation of the synthesis involves an intramolecular aryne-furan cycloaddition is the synthesis of several of the mansonone series by Best *et al.*⁸⁶⁻⁸⁸ The aryne precursor **129** utilised was either the diazonium chloride ($R^1 = \text{CO}_2\text{H}$, $R^2 = \text{N}_2^+\text{Cl}^-$) or the dibromide ($R^1 = R^2 = \text{Br}$) and gave a reasonable yield of cycloadduct **130**. In this instance, naphthalene **131**, as opposed to the naphthol, was the desired product, and treatment with diiron nonacarbonyl effected this transformation. This intermediate could then be converted to mansonone I (**132**) or mansonones E, F, or structurally similar biflorin.



Reagents and conditions: a) *n*-BuLi, Et₂O, -70 °C to 23 °C, 2 h, 61% or propylene oxide, DCE, Δ, 18 h, 92%; b) Fe₂(CO)₉, PhH, Δ, 6 h, 85%.

Scheme 27: Aryne-Furan Cycloaddition in the Synthesis of Mansonone I, **132**

Another key transformation was achieved using an aryne-furan cycloaddition in the synthesis of ventilone A (**136**) by Wege *et al.*⁸⁹ The diazo-carboxylate **133** was heated with furan **134** and cycloaddition and spontaneous aromatisation of the cycloadduct occurred to yield naphthol **135** (Scheme 28). This was subsequently transformed into ventilone A (**136**).



Reagents and conditions: a) propylene oxide, DCE, Δ, 10 min, 70%

Scheme 28: A Key Transformation in the Synthesis of Ventilone A

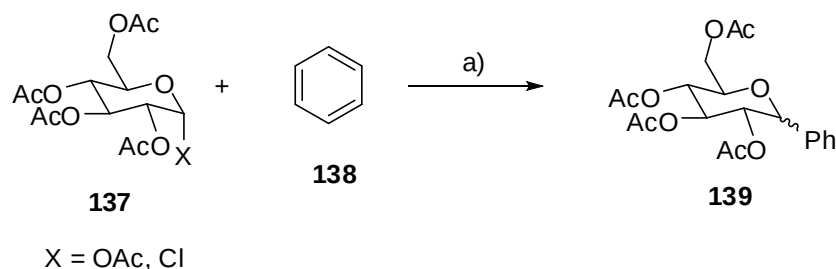
These examples demonstrate the usefulness of aryne-furan Diels-Alder reactions in synthesis. They are a convenient and usually high-yielding method for annelating highly-functionalised rings and despite the extreme reactivity of the aryne intermediate, it can tolerate a range of functionalities. Highlighted were their uses in natural product total synthesis, but the aforementioned reviews detail many other synthetically useful examples.

Chapter 3: Introduction - C-Aryl Glycosidation and its Application in Total Synthesis

Sch 47554 and Sch 47555 are both C-aryl glycosides, a class of natural products that are of interest due to their wide range of antibiotic activity and resistance to enzymatic hydrolysis. The most common method of synthesising C-aryl glycosides is by C-glycosidation with a glycosyl donor and an aromatic core as an acceptor, but the synthesis of C-aryl glycosides has progressed rapidly in recent years. A wide range of methodology has been developed, and an overview of the more relevant methods is presented here.

3.1 Overview of the Different Methods to Synthesise C-Aryl Glycosides

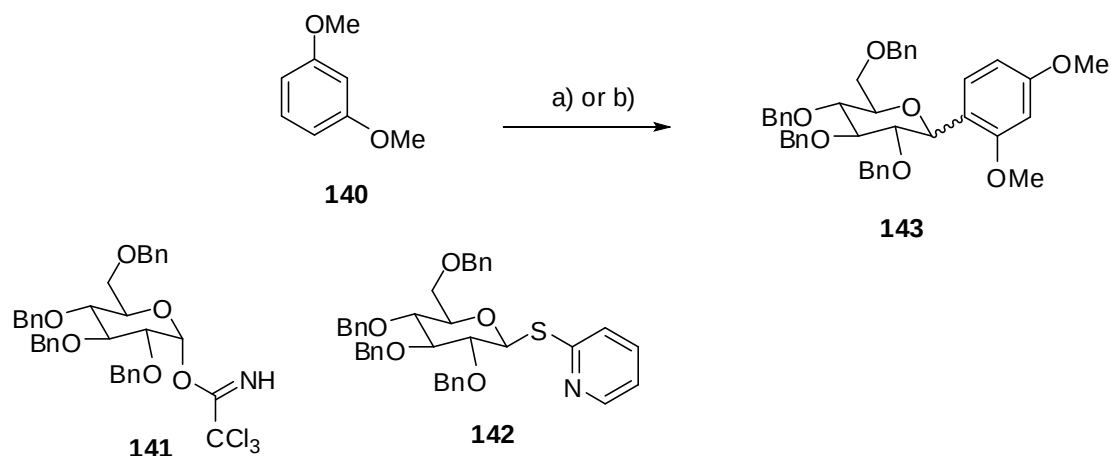
The very first C-aryl glycosides were synthesised by a Friedel-Crafts type reaction on benzene by Bonner *et al.* in 1945⁹⁰ with the very strong Lewis acid aluminium trichloride with glycosyl donors **137**, resulting in formation of C-aryl glycoside **139** in low yield.



Reagents and conditions: a) AlCl₃, variable yields

Scheme 29: The First C-Aryl Glycosidation

Nevertheless, the result was a pioneering one and methodology was further developed in later years, such as the use of electron donating groups to activate the aromatic system and enable the use of milder Lewis acids, such as zinc(II) oxide.⁹¹ Different glycosyl donors were developed for the reaction, such as Schmidt's use of trichloroacetimidates⁹² (e.g. **141**) or Williams's use of pyridyl thioglycosides (e.g. **142**).⁹³

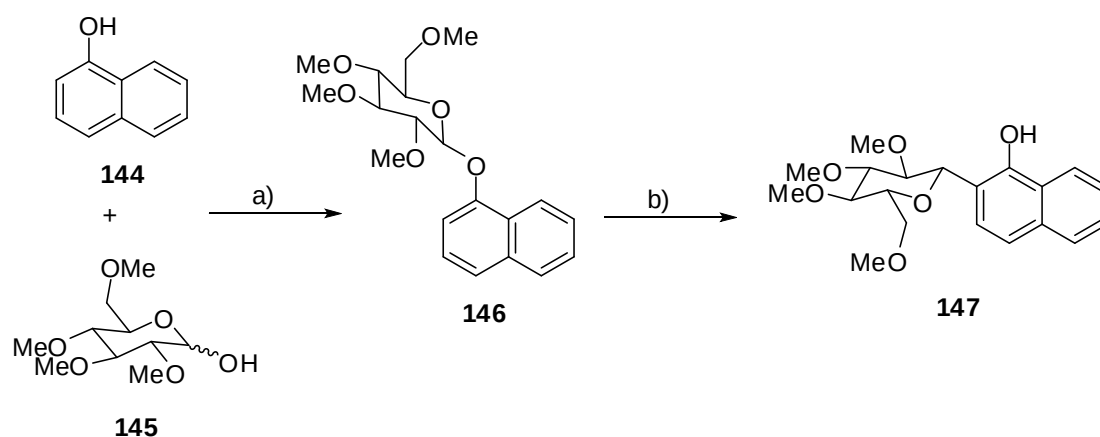


Reagents and conditions: a) 1 eq. $\text{BF}_3 \cdot \text{OEt}_2$, **141**, CH_2Cl_2 , 75% (only β); b) 1 eq. AgOTf , **142**, CH_2Cl_2 , 48% (only α).

Scheme 30: Early C-Aryl Glycosidation Reactions

The Schmidt system is notable for its improved yield and mild conditions for activation. It has high β -selectivity which is normal for pyranose-based glycosyl donors, as the β -anomer is the more stable (though with furanoses, the energy difference between the two anomers is much smaller and often mixtures of anomers are obtained). Therefore, the Williams donor is notable for its exclusive α -selectivity in certain solvents, despite the lower yield.

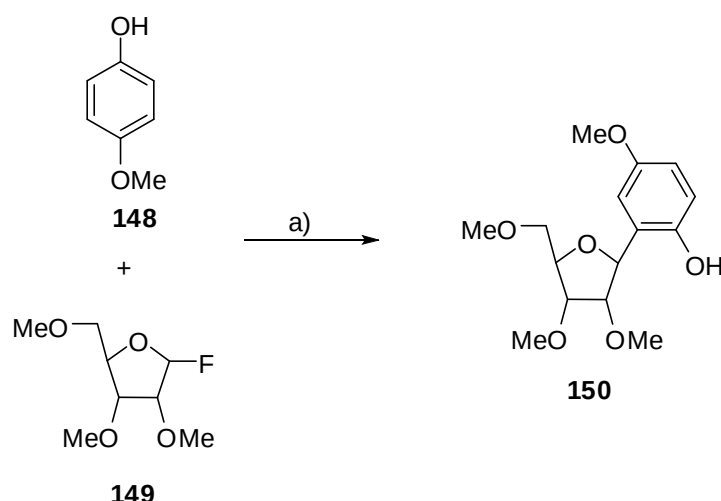
The first two examples of a new method of synthesising C-aryl glycosides taking advantage of an O- to C-glycosyl transfer were independently discovered within a short time of each other. Kometani *et al.*⁹⁴ discovered that by treating O-glycoside **146**, obtained from the Mitsunobu reaction between naphthol **144** and hemiacetal **145**, with boron trifluoride diethyl etherate, a rearrangement took place to give C-glycoside **147**, albeit in modest yield.



Reagents and conditions: a) PPh_3 , DEAD, THF, 15 h, 66%; b) $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , 4 h, 48%

Scheme 31: The Synthesis of C-Aryl Glycosides by Boron Trifluoride-Mediated O $\rightarrow$ C Transfer

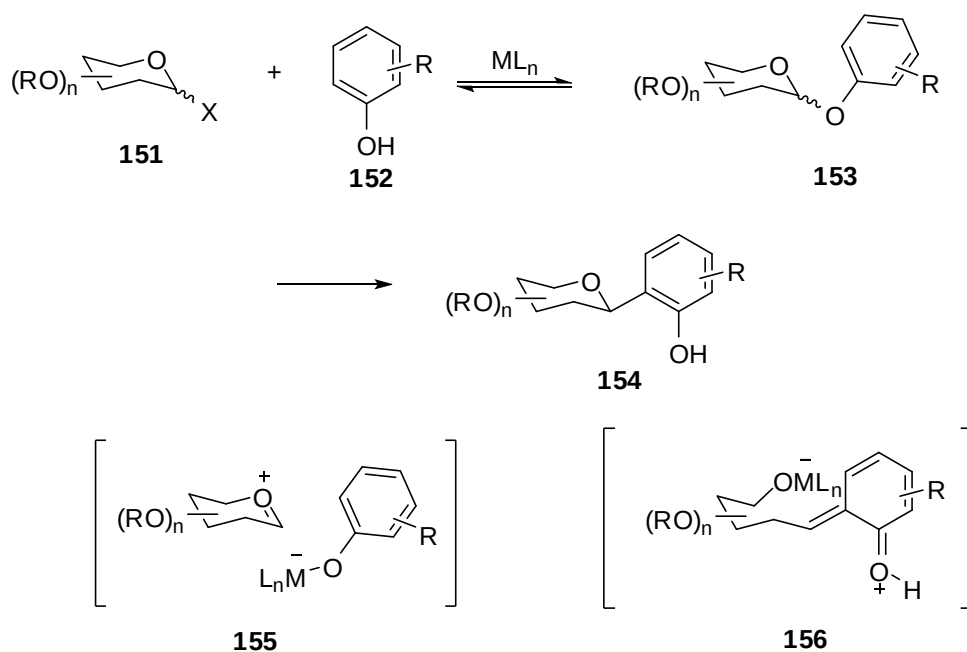
Meanwhile, Suzuki *et al.*⁹⁵ had developed similar methodology, whereby phenol **148** and glycosyl fluoride **149** were exposed to the Lewis acid system of hafnocene dichloride and silver perchlorate to give C-aryl glycoside **150** (Scheme 32). This system has many advantages over the Kometani one, specifically the yield is greater for a range of substrates tested and the reaction is one-pot, though the glycosyl fluoride does need to be separately synthesised.⁹⁶



Reagents and conditions: a) 1.5 eq. Cp_2HfCl_2 , 1.5 eq. AgClO_4 , 4Å MS, CH_2Cl_2 , -78°C to rt, 77% (10:1 β : α).

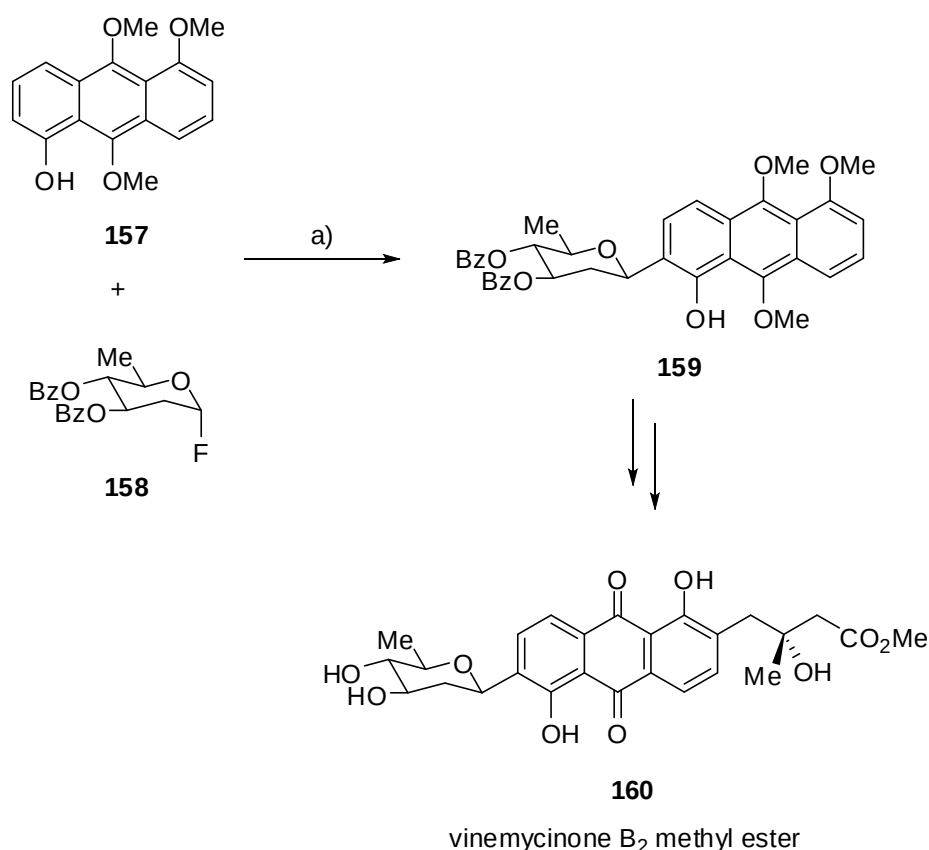
Scheme 32: Suzuki's Improved One-Pot Synthesis of C-Aryl Glycosides by O to C Transfer

The mechanism by which the *O*- to *C*-glycosidation proceeds and is able to form the β -anomer exclusively is detailed in Scheme 33.⁹⁷ The glycoside and phenol derivatives are mixed at low temperature to form the *O*-glycoside **153**. Upon warming, the glycosyl moiety is transferred to the carbon centre *via* a Friedel-Crafts-type coupling between the ion pair **155**. The *O*-glycoside formation is reversible, whereas the formation of the *C*-glycoside is irreversible and is regioselective for the *ortho*-position, a notable feature of this reaction. The β -anomer is thermodynamically favoured, and the kinetic product can be equilibrated *via* the *ortho*-quinone methide species **156**, a transformation which the Lewis acid system employed within is particularly effective at promoting.



Scheme 33: Mechanistic Aspects of the Hafnocene Dichloride-Silver Perchlorate-Promoted *C*-Aryl Glycosidation

The applicability of this methodology was demonstrated by Suzuki *et al.*⁹⁷ in the synthesis of vinemycinone B₂ methyl ester (**160**) (Scheme 34).



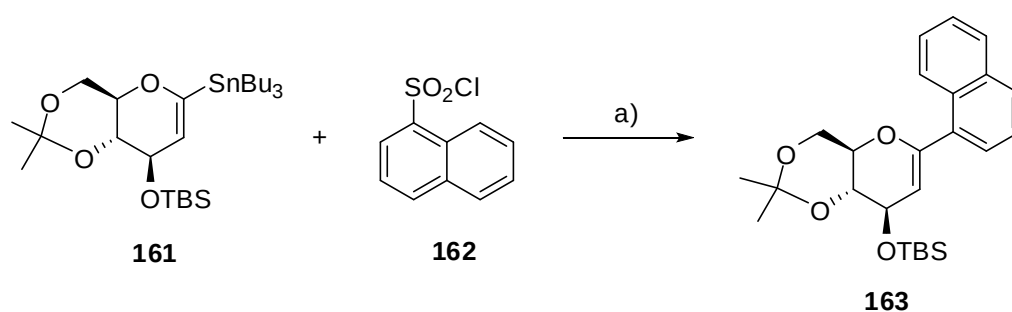
Reagents and conditions: a) 1.5 eq. Cp₂HfCl₂, 1.5 eq. AgClO₄, 4Å MS, CH₂Cl₂, -78 °C to rt, 86% (only β).

Scheme 34: Suzuki's Application of Aryl C-Glycosidation in Total Synthesis of Vinemycinone B₂ Methyl Ester (**160**)

Since this system was developed, many more Lewis acid systems have been explored to effect this transformation, such as boron trifluoride,⁹⁸ tin tetrachloride,⁹⁹ trimethylsilyl triflate (with or without silver perchlorate)¹⁰⁰ and scandium triflate,¹⁰¹ the choice of which depends on the desired stereoselectivity, type of glycosyl donor and compatibility with the substrates used. However it is also relevant that the type of glycosyl donor itself can influence the stereoselectivity, as can the solvent employed.¹⁰²

Other methods to synthesise C-aryl glycosides also exist and have been used effectively in synthesis but an exhaustive review of these methods is outside the scope of this section. A few examples are presented for illustration; more comprehensive reviews have been made.¹⁰³⁻¹⁰⁶

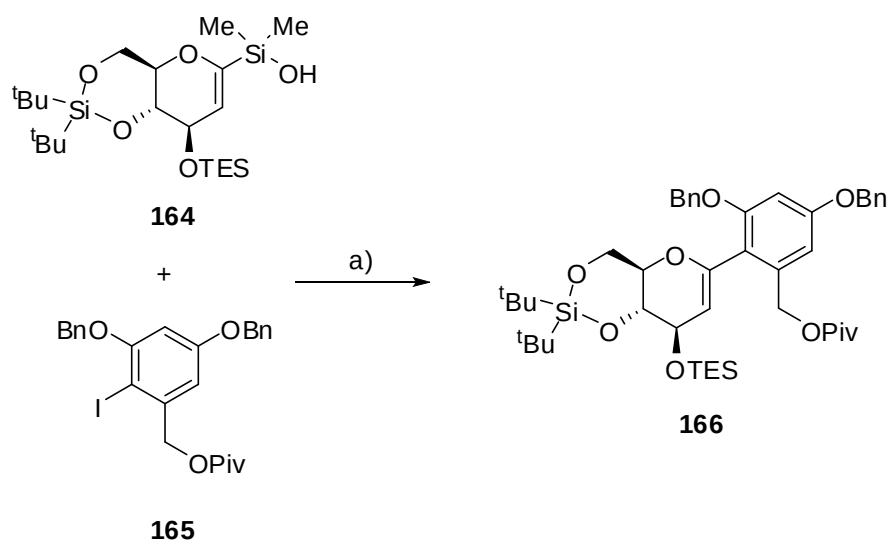
The use of palladium cross-coupling reactions is the most common of the other methods to synthesise C-aryl glycosides. An unusual example is the synthesis of C-aryl glycosides from tin glycals, such as **161** with sulfonyl chlorides using the Stille coupling.¹⁰⁷ Using tri-2-furylphosphine (TFP) as a ligand and a copper bromide additive, the reaction proceeds in a reasonable yield of 69% (Scheme 35).



Reagents and conditions: a) 5 mol% $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$, 18 mol% TFP, 10 mol% $\text{CuBr} \cdot \text{SMe}_2$, THF, Δ , 12 h, 69%.

Scheme 35: C-Aryl Glycoside Formation by Desulfatative Stille Cross-Coupling of Tin Glycals with Sulfonyl Chlorides

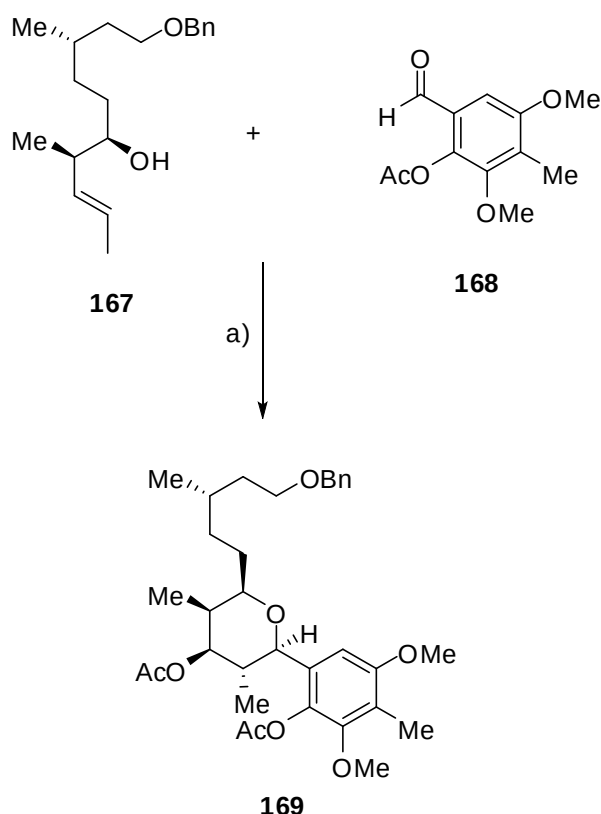
Another interesting example is the coupling between silanol **164** and aryl iodide **165** in the total synthesis of papulacandin D by Denmark *et al.*^{108,109} (Scheme 36). The coupling proceeds in high yield (82%) under mild conditions.



Reagents and conditions: a) $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$, NaOt-Bu , PhMe, 50 °C, 82%.

Scheme 36: Palladium Catalysed Silanol-Iodide Coupling in the Total Synthesis of Papulacandin D

Aside from palladium-catalysed couplings, other methods have recently been developed. An elegant example is the synthesis of a *C*-aryl glycoside *via* the Prins reaction between alcohol **167** and benzaldehyde derivate **168** by Rychnovsky *et al.*¹¹⁰ (Scheme 37). The glycoside **169** was obtained in good yield as a single diastereomer under the conditions used. This intermediate was successfully elaborated upon in a formal total synthesis of kendomycin.



Reagents and conditions: a) $\text{BF}_3 \cdot \text{OEt}_2$, AcOH, *n*-hexane, 0 °C to rt, 65%.

Scheme 37: *C*-Aryl Glycoside Formation *via* a Prins Reaction in Rychnovsky's Formal Total Synthesis of Kendomycin

These examples are a small fraction of a range of methodology that has been applied to the synthesis of the *C*-aryl glycoside motif and other methods include, *inter alia*, Negishi cross-coupling between arylzinc species and glycosyl bromides,¹¹¹ Heck cross coupling between aryl iodides and glycals,¹¹² attack on quinone species by lithiated glycosides to give a *para*-glycoside,¹¹³ cycloadditions between glycosyl dienes and quinones,^{114,115} ruthenium (II)-catalysed 2+2+2 cycloadditions,¹¹⁶

uncatalysed reactions between triaryliindium species and glycals¹¹⁷ and reaction of aryl nitrile oxides with alkynols resulting in a *de novo* glycoside formation.¹¹⁸

3.2 Synthesis of C-glycosides with Aryne Chemistry

With the use of aryne-furan cycloadditions and glycosidations on the subsequent naphthol products in the synthesis of C-aryl glycosides having being established, Martin *et al.* examined the scope and generality of their use for each of the four major classes of C-aryl glycoside (Figure 5).¹¹⁹ As this encompasses the use of aryne-furan cycloadditions in the formation of C-aryl glycosides, they will be examined in more detail.

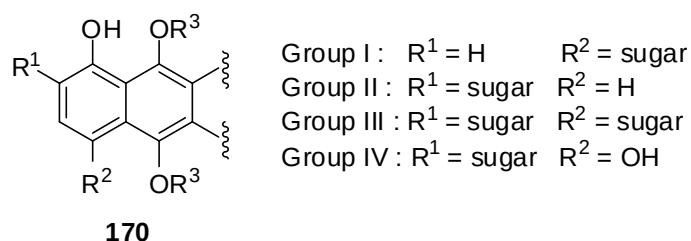
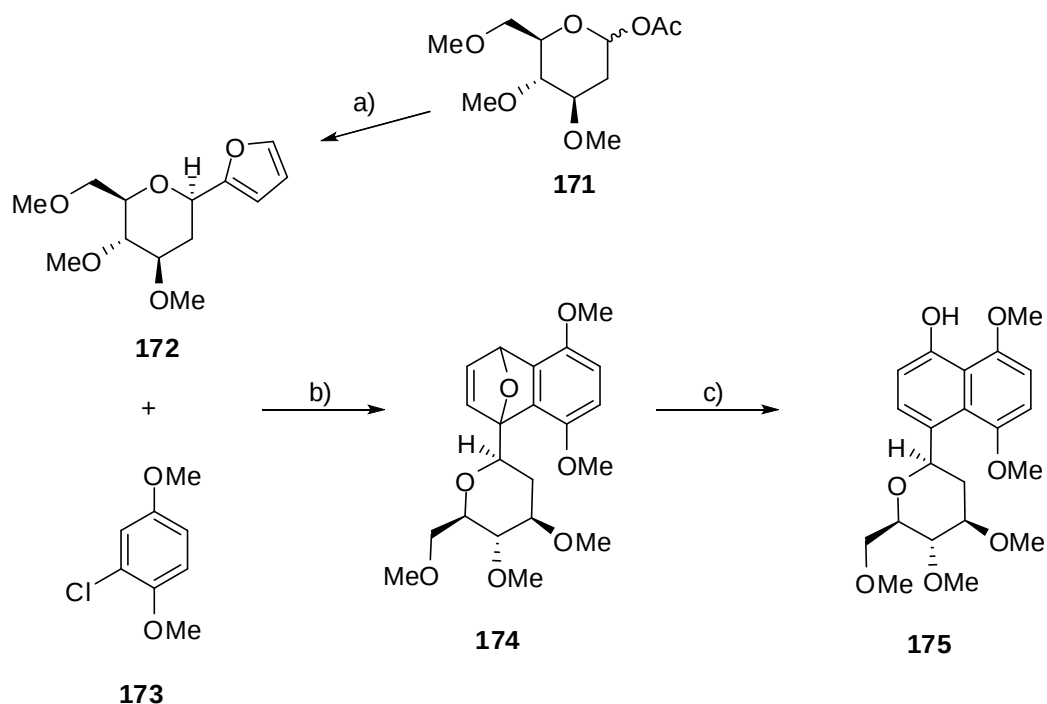


Figure 5: Classification of C-Aryl Glycosides

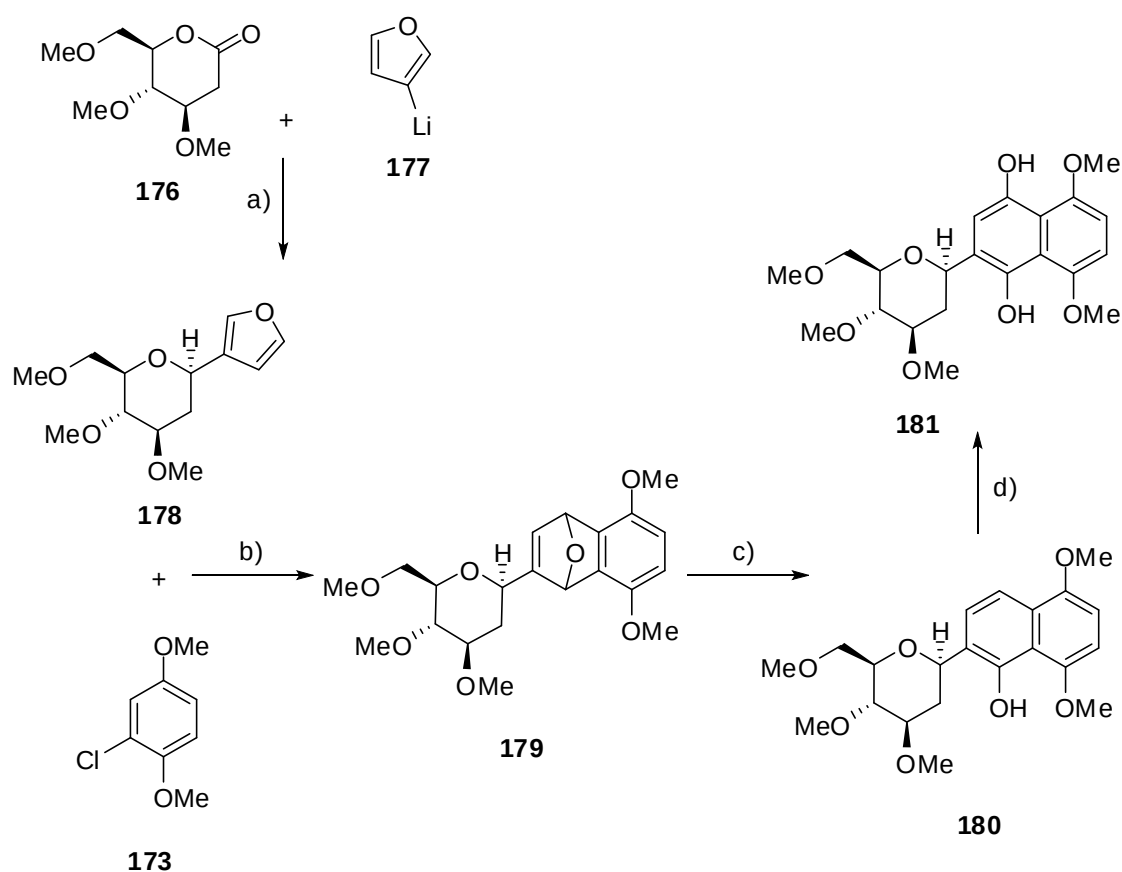
The Group I C-aryl glycosides were made in a concise three-step sequence. Glycosyl acetate **171** was treated with furan in the presence of boron trifluoride diethyl etherate. This effectively C-glycosidated furan to give glycosylfuran **172**, which was allowed to react with the aryne derived from chloride **173** to give the corresponding cycloadduct **174**. This was then aromatised under acidic conditions to give the naphthol **175** in excellent yield (Scheme 38).



Reagents and conditions: a) furan, $\text{BF}_3 \cdot \text{OEt}_2$, 74%; b) *sec*-BuLi, -95°C to rt, 85%; c) TFA, 98%.

Scheme 38: Synthesis of a Group I C-Aryl Glycoside

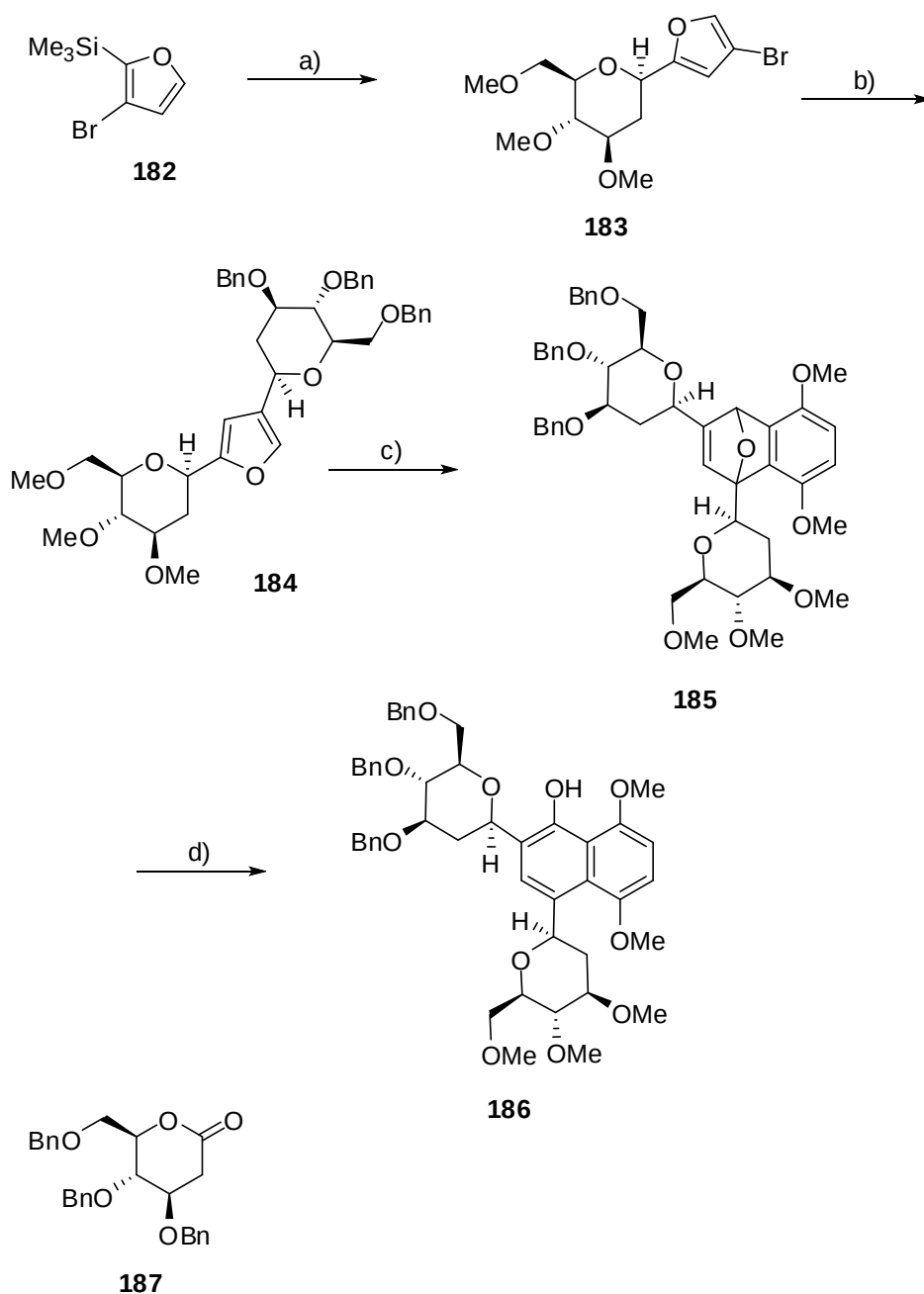
The Group II C-glycosides were accessed by a similar reaction, with the same aryne precursor **173**, but a 3-substituted furan, **178**, which was synthesised by treating 3-lithiofuran (**177**) with lactone **176**. The cycloadduct was aromatised with acid again to produce the Group II C-aryl glycoside **180**, along with the *meta*-isomer. The Group IV glycoside **181** can be obtained from the Group II one by oxidation to the quinone with iodobenzene diacetate and reduction with sodium dithionite (Scheme 39).



Reagents and conditions: a) i) -78°C to rt ii) NaCNBH_3 , EtOH/HCl , 51%; b) *sec*- BuLi , -95°C to rt, 91%; c) TFA , 97%; d) i) $\text{PhI}(\text{OAc})_2$, ii) $\text{Na}_2\text{S}_2\text{O}_4$, 70%.

Scheme 39: Synthesis of Group II (**180**) and IV (**181**) C-Aryl Glycosides

The more challenging Group III glycosides were also synthesised successfully by Martin *et al.* Synthesis of 2,4-diglycosylfuran **184** was made possible with the use of furan **182** and sequential lithiation and quenching with lactones **176** and **187**. This furan was then subjected to the aryne derived from chloride **173** and the expected cycloadduct **185** was obtained. This could then be aromatised with acid to give the Group III glycoside **186** (Scheme 40).

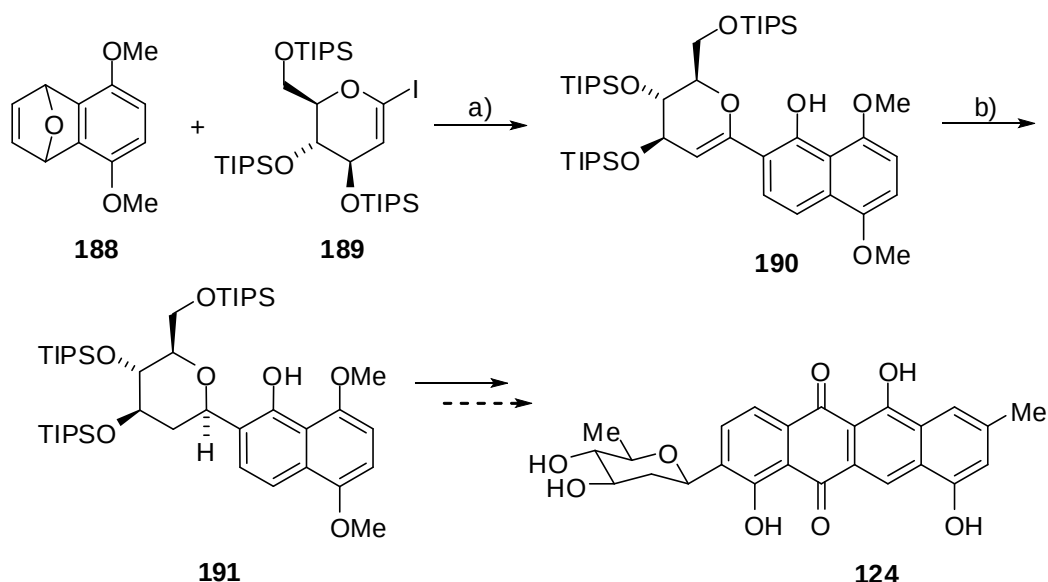


Reagents and conditions: a) i) LDA, THF ii) **176**, iii) NaCNBH₃, EtOH, HCl, 55%; b) i) *n*-BuLi, THF ii) **187**, iii) NaCNBH₃, EtOH, HCl, 58%; c) **173**, *sec*-BuLi, -95 °C to rt, 81%; d) TFA, 87%.

Scheme 40: Synthesis of Group III C-Aryl Glycosides

Another approach Martin *et al.* attempted to develop¹¹⁹ was that of opening initial cycloadduct **188** with a glycosyl carbanion by a S_N2' reaction, which had precedent with non-glycosidic carbanions,¹²⁰ to yield naphthol **190**. However, for all the systems tried, no significant quantities of desired ring-opened product were isolated. Therefore, an alternative procedure, involving the palladium-catalysed reaction of

iodoglycals with such cycloadducts was investigated.¹²¹ Reaction of iodoglycal **189** with cycloadduct **188** under the conditions developed gave a 1:1 mixture of diastereomeric *cis*-dihydronaphthols, which could be oxidised, using DDQ and hydrogenated to give naphthol **191** (Scheme 41). Martin *et al.* then utilised a system similar to **191** in a formal total synthesis of galtamycinone (**124**).¹²²

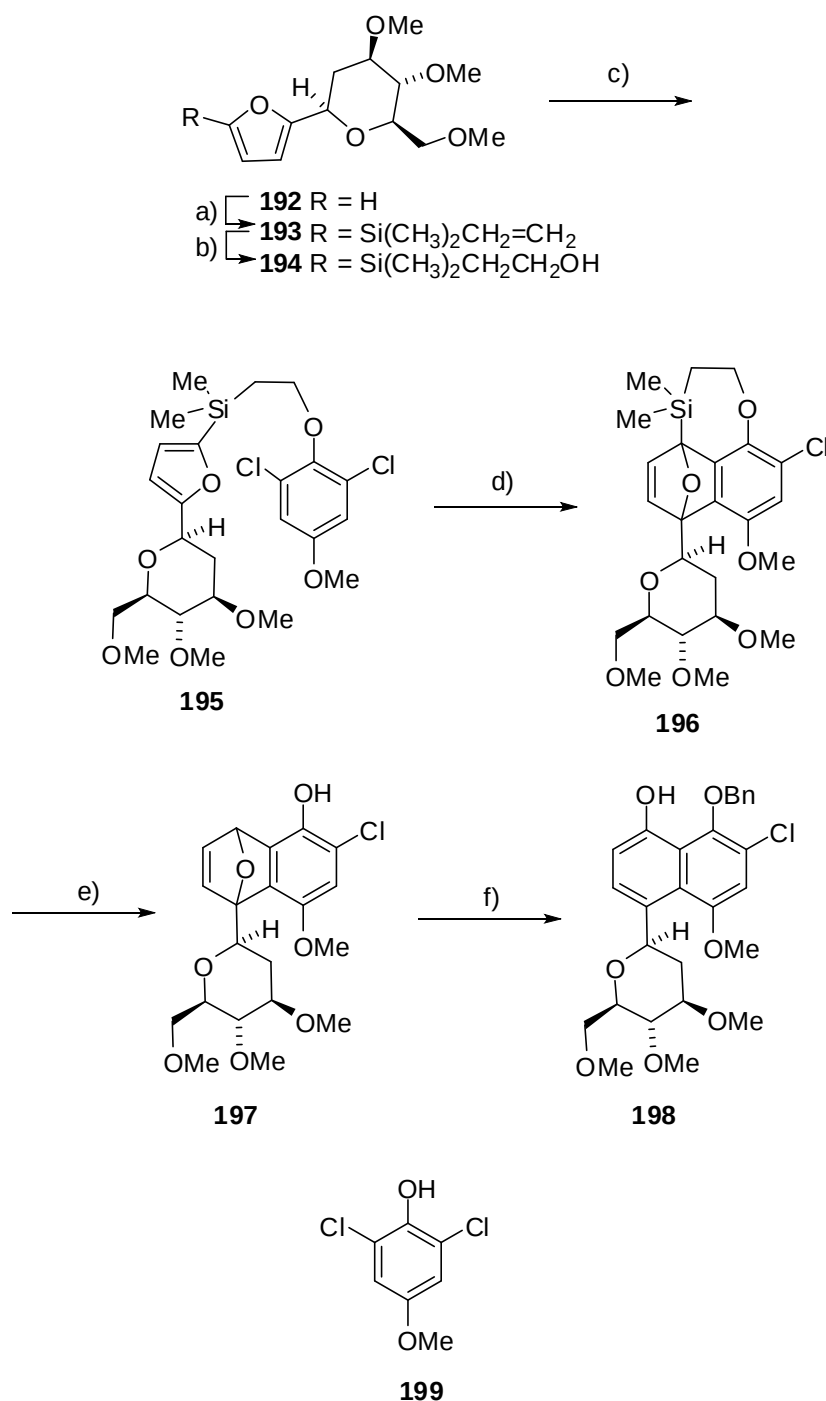


Reagents and conditions: a) i) $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, NEt_3 , Zn , ZnCl_2 , THF, 50 °C; ii) DDQ, dioxane, Δ , 50%; b) H_2/PtO_2 , 85%.

Scheme 41: Conversion of Cycloadduct **188** to Group II C-Aryl Glycoside **191**

All the approaches described thus far utilise symmetrical arynes, so the regiochemistry of cycloaddition was not an issue. Typically though, for cycloadditions between unsymmetrical arynes and unsymmetrical furans, the regioselectivity is poor. Therefore, to control the regioselectivity of the benzyne-furan reactions leading to the major groups of C-aryl glycosides, disposable silicon tethers were employed by Martin *et al.*¹²³ The 2-glycosyl furan **192** was deprotonated and quenched with chlorodimethylvinylsilane to yield furan **193**. This was hydroborated regioselectively and oxidised to give the silyl alcohol **194**. Mitsunobu coupling of **194** with 2,6-dichloro-4-methoxyphenol delivered aryl chloride **195**. The aryne was generated and underwent intramolecular cycloaddition with the furan moiety to afford the cycloadduct **196**, which could be desilylated with TBAF in DMF, and ring-opened with acid catalysis to deliver the Group I C-aryl glycoside **197** (Scheme 42). In some

cases a one-carbon tether was possible, in which case the $\text{-CH}_2\text{Br}$ silane could be used instead of the vinyl silane, shortening the synthesis, however it was not generally applicable. This methodology, with the relevant variations, was also applied to successfully synthesise Group II and III glycosides in a similar manner.

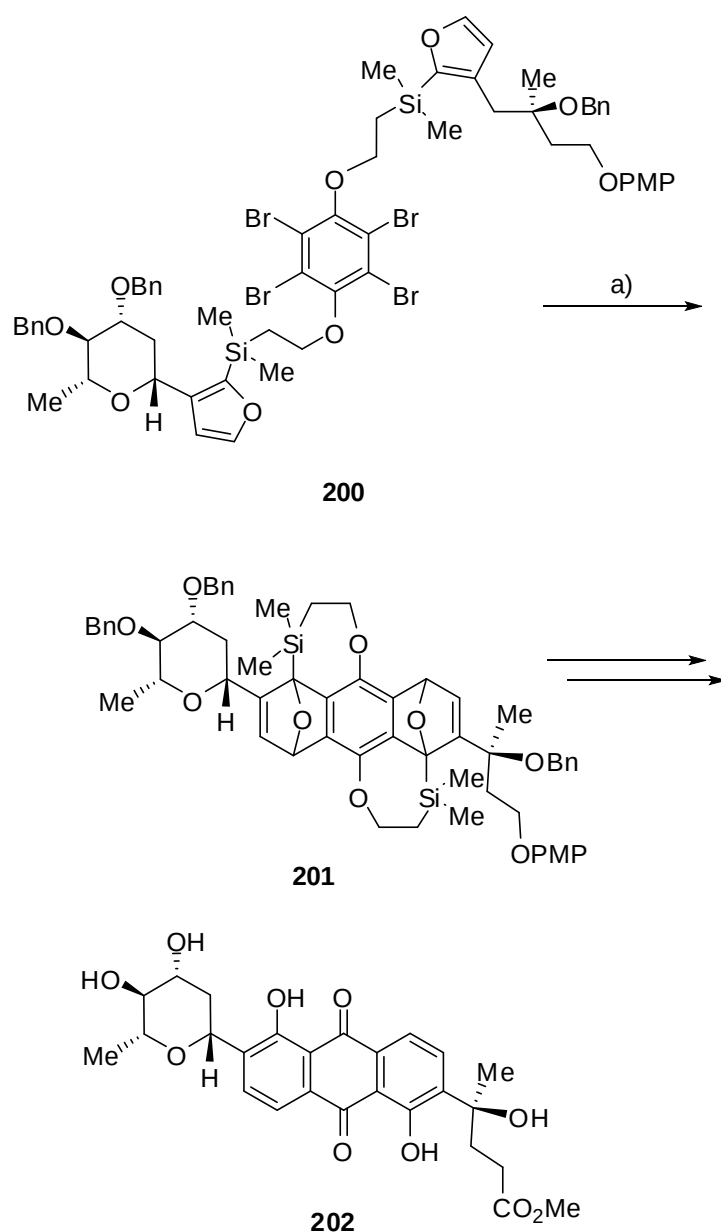


Reagents and conditions: a) *n*-BuLi, THF, $-78\text{ }^\circ\text{C}$; $\text{Me}_2\text{SiCl}(\text{CH}=\text{CH}_2)$, 88%; b) i) 9-BBN, THF; ii) H_2O_2 , NaOH, 88%; c) **199**, DIAD, PPh_3 , THF, 75%; d) *t*-BuLi, THF, $-95\text{ }^\circ\text{C}$ to $-10\text{ }^\circ\text{C}$, 81%; e) *n*-Bu₄NF, DMF, $70\text{ }^\circ\text{C}$, 80%; f) i) NaH, BnBr, 95%; ii) TFA, CH_2Cl_2 , 90%.

Scheme 42: The Synthesis of Group I C-Aryl Glycoside **198** Using a Silicon Tether

Further investigations into the field of silyl-tethered intramolecular aryne-furan cycloadditions led to Martin *et al.* developing a double aryne-furan precursor **200**,

synthesised by two Mitsunobu reactions as before. Upon treatment with 3 equivalents of *n*-butyllithium, the arynes were sequentially generated and the tandem cycloadditions occurred giving the double cycloadduct **201** in 85% yield. This substrate was further elaborated, steps including aromatisation and silyl linker cleavage, to give vineomycinone B₂ methyl ester (**202**).



Reagents and conditions: a) *n*-BuLi, -20 °C, Et₂O, 85%.

Scheme 43: Double Intramolecular Aryne-Furan Cycloaddition in Martin's Synthesis of Vineomycinone B₂ methyl ester (**202**)

Chapter 4: Project Objective and Previous Results

4.1 Initial Project Objective

Given the synthetic challenge, and the interesting biological activities of Sch 47554 and Sch 47555, a total synthesis program was instigated in the group. The key synthetic concept in the envisaged strategy was a two-directional aryne-furan Diels-Alder cycloaddition between a diaryne equivalent, **203**, and appropriate furan-containing moieties to furnish a polycyclic compound. It was envisaged that a simple reagent for the dibenzyne synthon is 1,4-dimethoxy-2,5-difluorobenzene, **204**, an atom-efficient starting material containing the fluorine substituent, known to be a good aryne precursor (Figure 6). The important feature of the aryne derived from lithiated aryl fluorides is that the intermediate is stable at low temperature and only forms the aryne on warming, so that the formation of arynes can be performed sequentially and is more easily controllable.

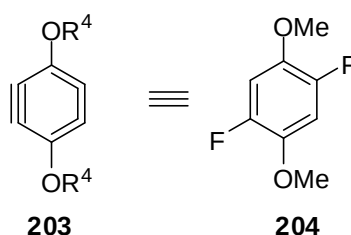
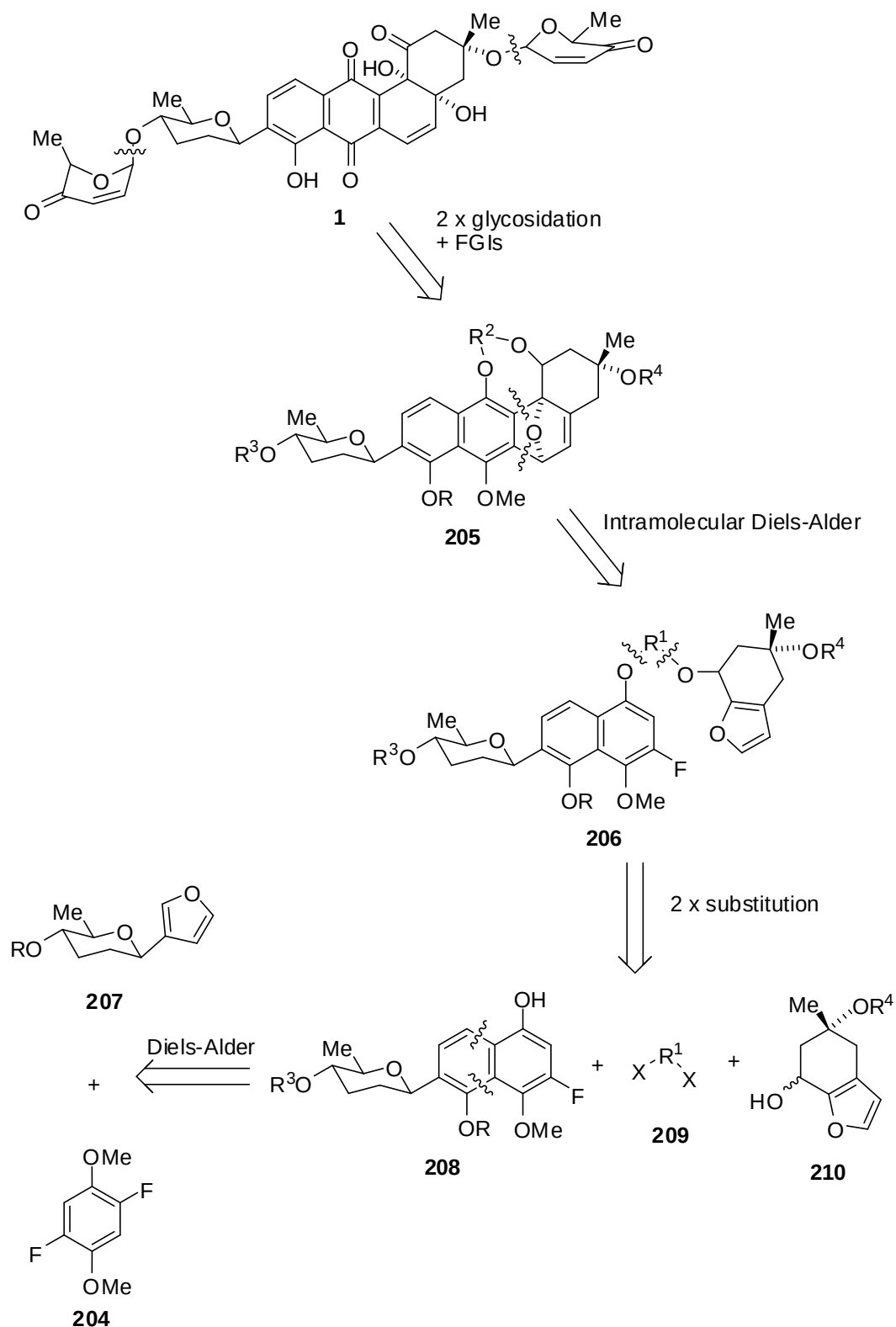


Figure 6: Diaryne **203** and Difluoride Precursor **204**

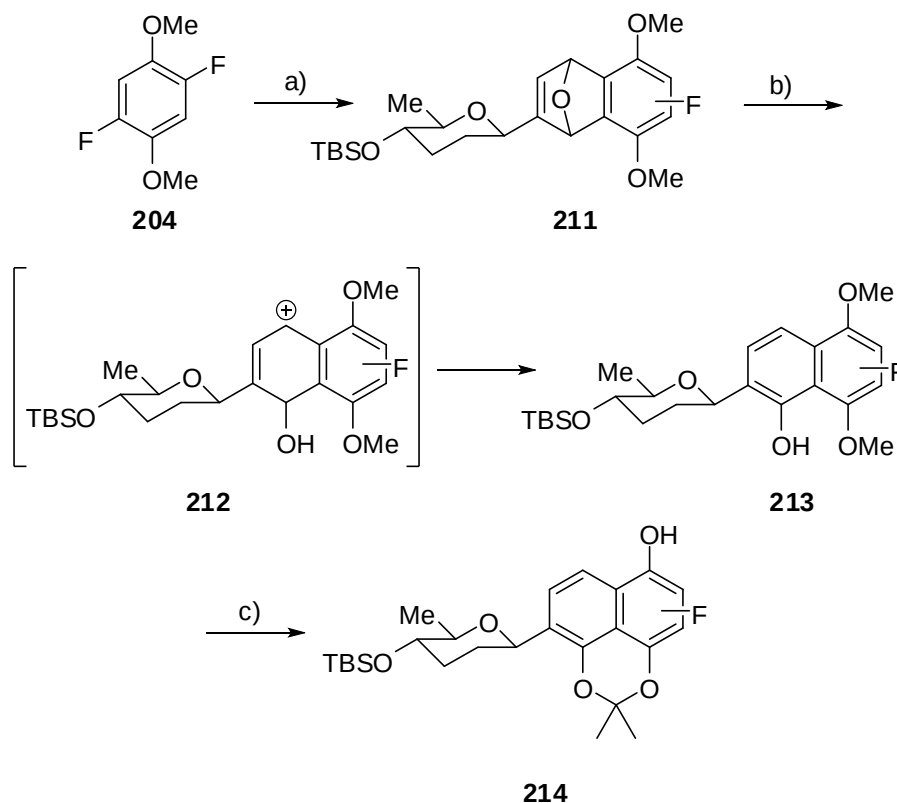
The retrosynthetic analysis is described in Scheme 44, where the two key cycloaddition reactions envisaged differ in that one is intramolecular, and one intermolecular. The intramolecular one, between rings A and C, creating ring B in the process, would be achieved using an oxygen-based linker to direct the ABC angularly-fused system into the correct orientation for the desired natural products.



Scheme 44: Retrosynthetic Analysis of **1**

The intermolecular cycloaddition would be carried out with a 3-glycosylfuran moiety and the benzyne formed *in situ* from 1,4-dimethoxy-2,5-fluorobenzene (**204**). It is

envisaged that the ring-opening aromatisation would proceed *via* the more stabilised carbocation intermediate, **212**, and thus give exclusively the desired naphthol, **213**, as shown in Scheme 45.

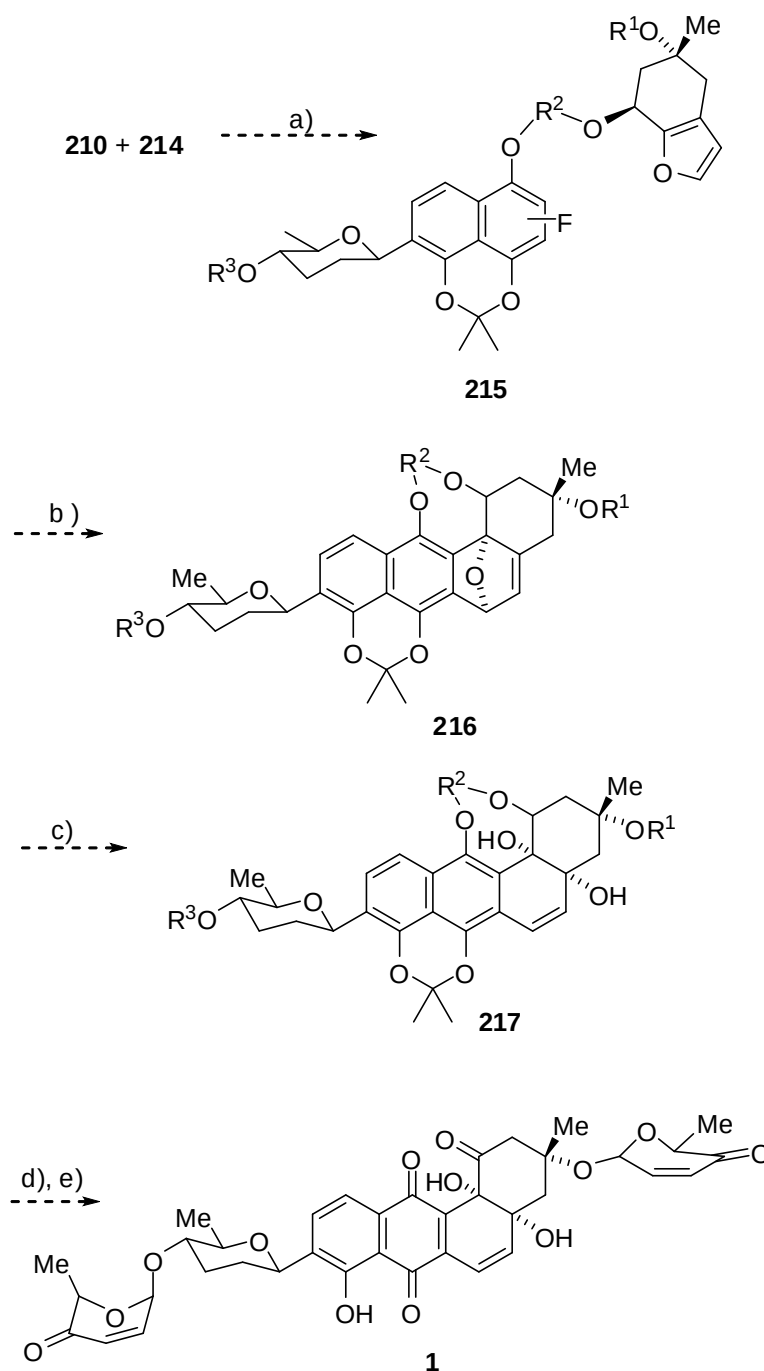


Reagents and conditions: a) i) *n*-BuLi, THF, -78°C ; ii) 3-glycosylfuran; b) aq. HCl, MeOH; c) i) oxidation, ii) $\text{Na}_2\text{S}_2\text{O}_4$, iii) 2,2-dimethoxypropane, TsOH, acetone

Scheme 45: Planned Synthesis of Left-Hand Side of Sch 47554

With this naphthol in hand, there would still be several steps needed in the synthesis of Sch 47554 (Scheme 46). The synthesis of furan **210** would need to be accomplished, and then linking it through its hydroxyl functionality to the phenol. The length of this linker may need to be changed to better facilitate the subsequent intramolecular step, e.g. to $-\text{OCR}_2\text{O}-$ or $-\text{OSiR}_2\text{O}-$. The second benzyne-furan Diels-Alder reaction can then be carried out, the tethering of the furan moiety ensuring the regioselectivity is such that the desired angularly-fused carbon skeleton is obtained. The palladium-catalysed $\text{cis-S}_{\text{N}}2'$ opening of the oxacyclic functionality¹²⁴ generated from the cycloaddition using a silyl zincate¹²⁵ and subsequent Tamao oxidation¹²⁶ is envisaged to lead to diol **217**. Deprotection and then two Ferrier-type

rearrangements¹²⁷ with the relevant sugar units and global oxidation, using CAN (e.g. in the formation of the quinone functionality in ring B), MnO₂ or Dess-Martin periodane are the remaining transformations required to furnish Sch 47554 (**1**).



Reagents and conditions: a) double substitution; b) aryne-furan Diels-Alder reaction; c) i) $\text{Li}[\text{ZnEt}_2(\text{SiMe}_2(i\text{-Pr}_2\text{N}))]$, $\text{PdCl}_2(\text{dppf})$, PhMe , THF ; ii) $m\text{-CPBA}$, KHF_2 , DMF ; d) i) deprotection, ii) O-glycosidation, iii) glycoside oxidation; e) aromatic oxidation.

Scheme 46: Planned Completion of Sch 47554 (**1**)

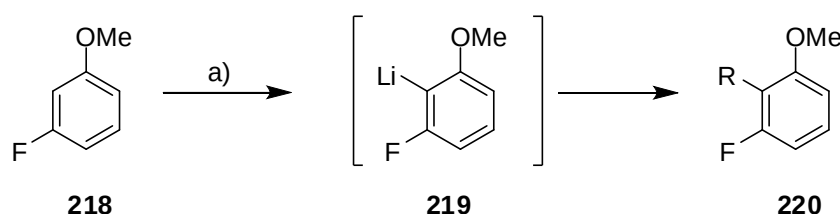
This stereoselective synthesis should provide a reliable and adaptable route to the desired compound, whilst also providing opportunities to introduce diversity; thus it should be amenable to the synthesis of analogues, so structure-activity relationships can be determined for this angucycline pharmacophore.

4.2: Previous Studies in the Group

Research has already been carried out on this project, and a summary of this work and its results and conclusions is described here.

4.2.1 Studies on the Double Benzyne-Diels Alder Reaction

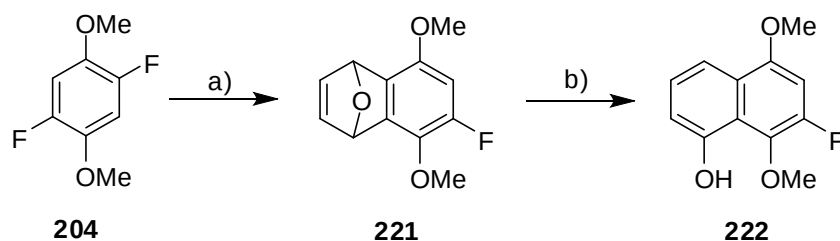
Firstly, it needed to be established that 1,4-difluoro-2,5-dimethoxybenzene (**204**) was a suitable precursor for the double aryne **203**. Lithiation has been shown to occur at C-2 in 3-fluoroanisole¹²⁸ and the carbanion trapped with a range of electrophiles, such as iodine, DMF or CO₂.



Reagents and conditions: a) i) *n*-BuLi, THF −78 °C, ii) E⁺, e.g. I₂, DMF, CO₂

Scheme 47: Lithiation and Electrophilic Trapping of Lithiated 3-Fluoroanisole

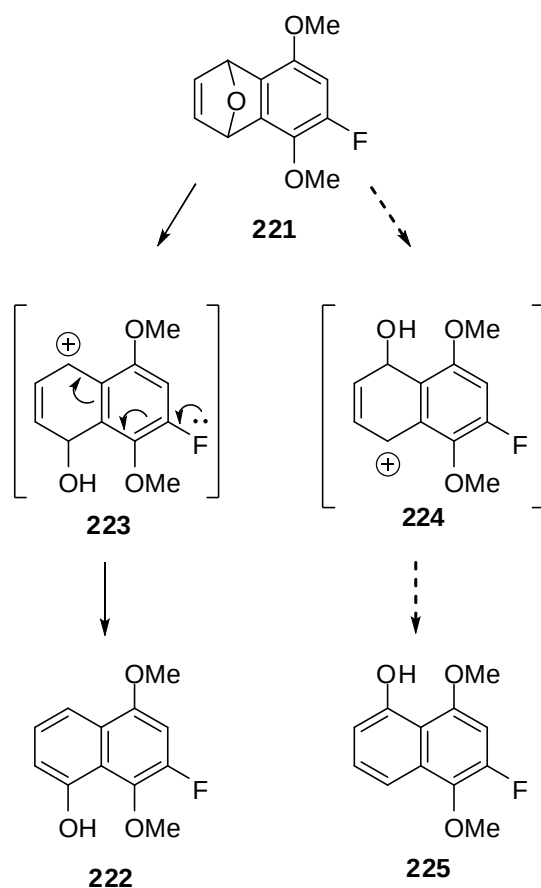
The reaction of difluoride **204** with *n*-butyllithium and subsequent quench with furan was expected to yield the cycloadduct **221**, and this product was indeed observed, in 80% yield when the solvent was tetrahydrofuran. The use of diethyl ether as the solvent led to side products resulting from addition of butyllithium to the cycloadduct. The cycloadduct could be aromatised under acidic conditions to furnish naphthol **222** in 86% yield, the structure of which was confirmed by X-ray crystallography.



Reagents and conditions: a) i) *n*-BuLi, THF -78 °C, 80%; ii) furan, 0 °C; b) aq. HCl, MeOH, 86%

Scheme 48: The Initial Aryne-Furan Diels-Alder Reaction with **204**

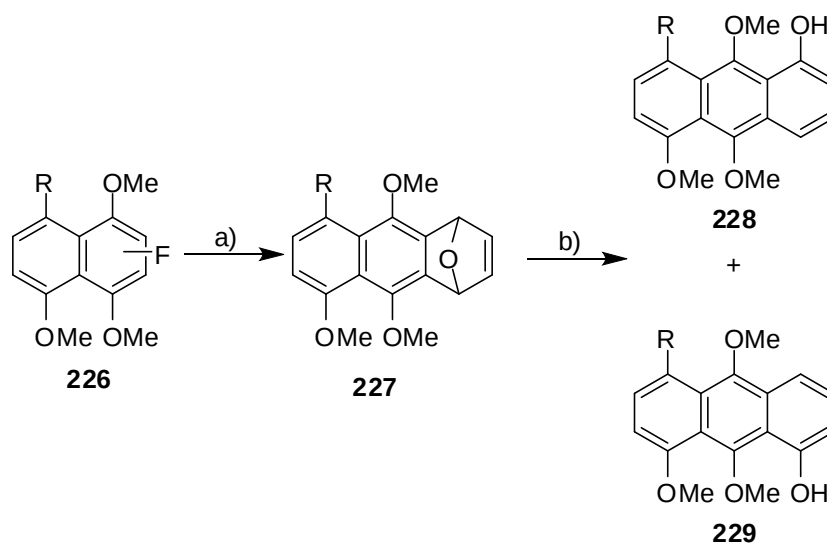
The potential regioisomer of **222** (i.e. **225**) was not observed, because of the stability conferred by the fluorine substituent on the carbocation intermediate following the breaking of the C-O bond, in the aromatisation.⁷⁵ For carbocation **223**, the fluorine stabilises the positive charge through resonance, but for carbocation **224**, no such stabilisation is possible (Scheme 49).



Scheme 49: Potential Regioisomers of the Aromatised Cycloadducts and their Carbocation Precursors

The methodology was extended to more functionalised furans, with substituents in the 2- or 3- positions, and in most cases it was possible to obtain the expected products in a varying ratio of regioisomers. In almost all cases, the regioisomers were separable, and characterisable by X-ray crystallography or NOESY spectroscopy.

After methylation of naphthol **222** and the other substituted naphthols examined, the second benzyne-furan reaction was examined for many of the derivatives (Scheme 50). Lithiation of fluorides **226**, benzyne formation and trapping with furan gave the corresponding cycloadducts **227** in high yields (61-88%). These were aromatised under acidic conditions to deliver the regioisomeric anthracenols **228** and **229** (often inseparable, 71-85%). This work was published in the *Journal of Organic Chemistry*.¹²⁹

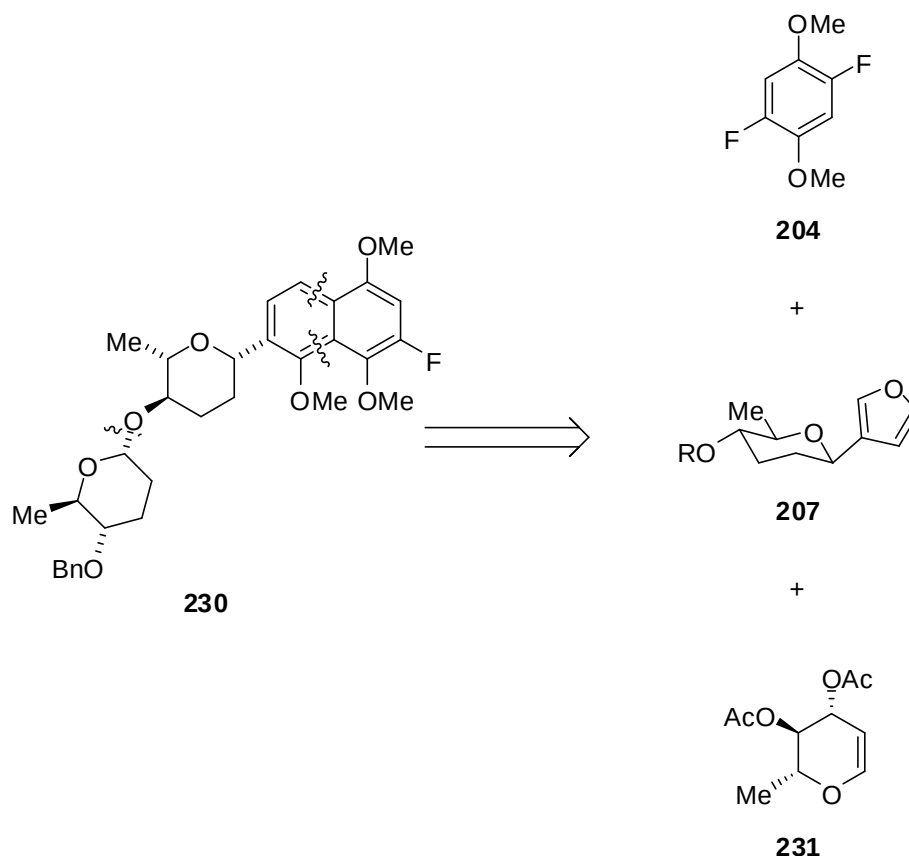


Reagents and conditions: a) i) *n*-BuLi, THF -78°C , ii) furan, 0°C , 61-88%; b) aq. HCl, THF, 71-85%

Scheme 50: Second Benzyne-Furan Diels-Alder Reactions

4.2.2 Studies Towards the Synthesis of the Left-Hand Side of Sch 47554 and Sch 47555

With this methodology established, attention was then turned to the synthesis of Sch 47554. The first molecule the group targeted was the disaccharide **230** and related compounds, starting from di-*O*-acetyl-L-rhamnal, **231**.

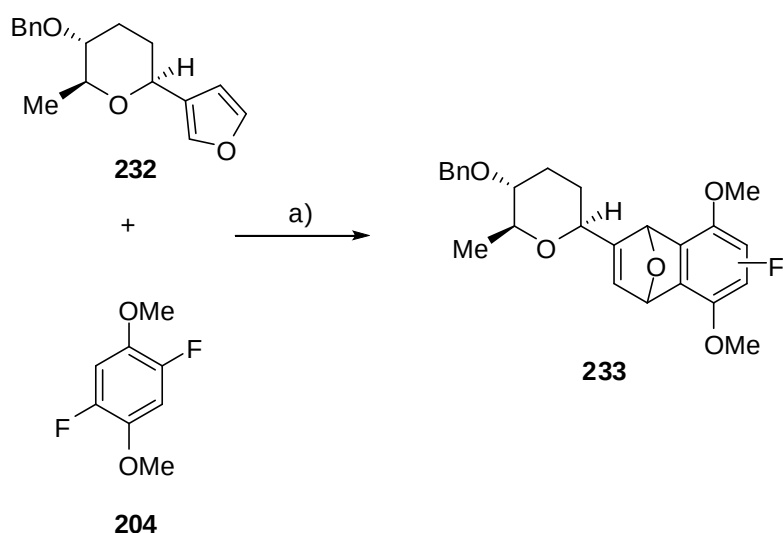


Scheme 51: Retrosynthetic Analysis of a Model Disaccharide

The reaction between aryne precursor **204** and suitably-protected 3-glycosylfuran **232** will give the cycloadduct and aromatisation will give the desired C-glycoside. The regioselectivity of the reaction is important here, the furan is not symmetrical and so can add either way to the aryne. If successful, the naphthol can be protected, the glycoside deprotected and the second glycosidic moiety appended.

However this route proved to be unsuccessful as the key aryne-furan cycloaddition, although high yielding, gave an equal mix of the possible regioisomers **233**. As has

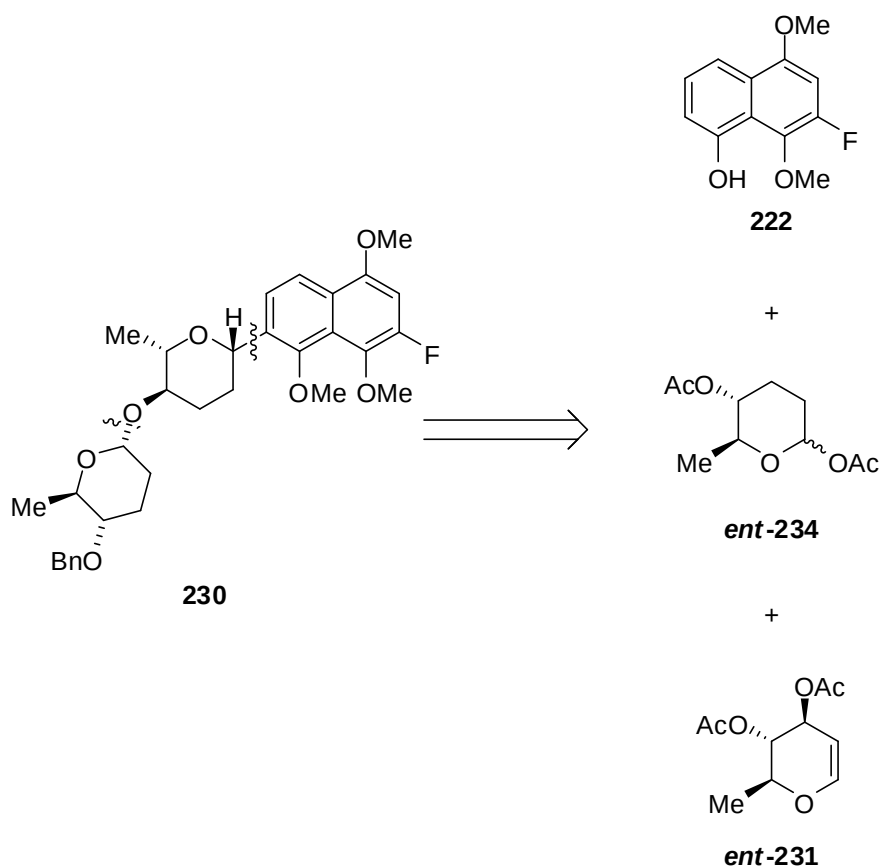
been discussed previously, this is a common feature of reactions featuring an unsymmetrical furan and unsymmetrical aryne, and given the reactive nature of the intermediate, the relatively minor difference between regioisomers and large distance between the fluoride and glycoside, it is unsurprising that no regioselectivity was obtained (Scheme 52).



Reagents and conditions: a) *n*-BuLi, THF, $-78\text{ }^{\circ}\text{C}$ to rt, 88% (1:1 mixture of regioisomers)

Scheme 52: The Aryne-(3-Glycosyl)furan Cycloaddition

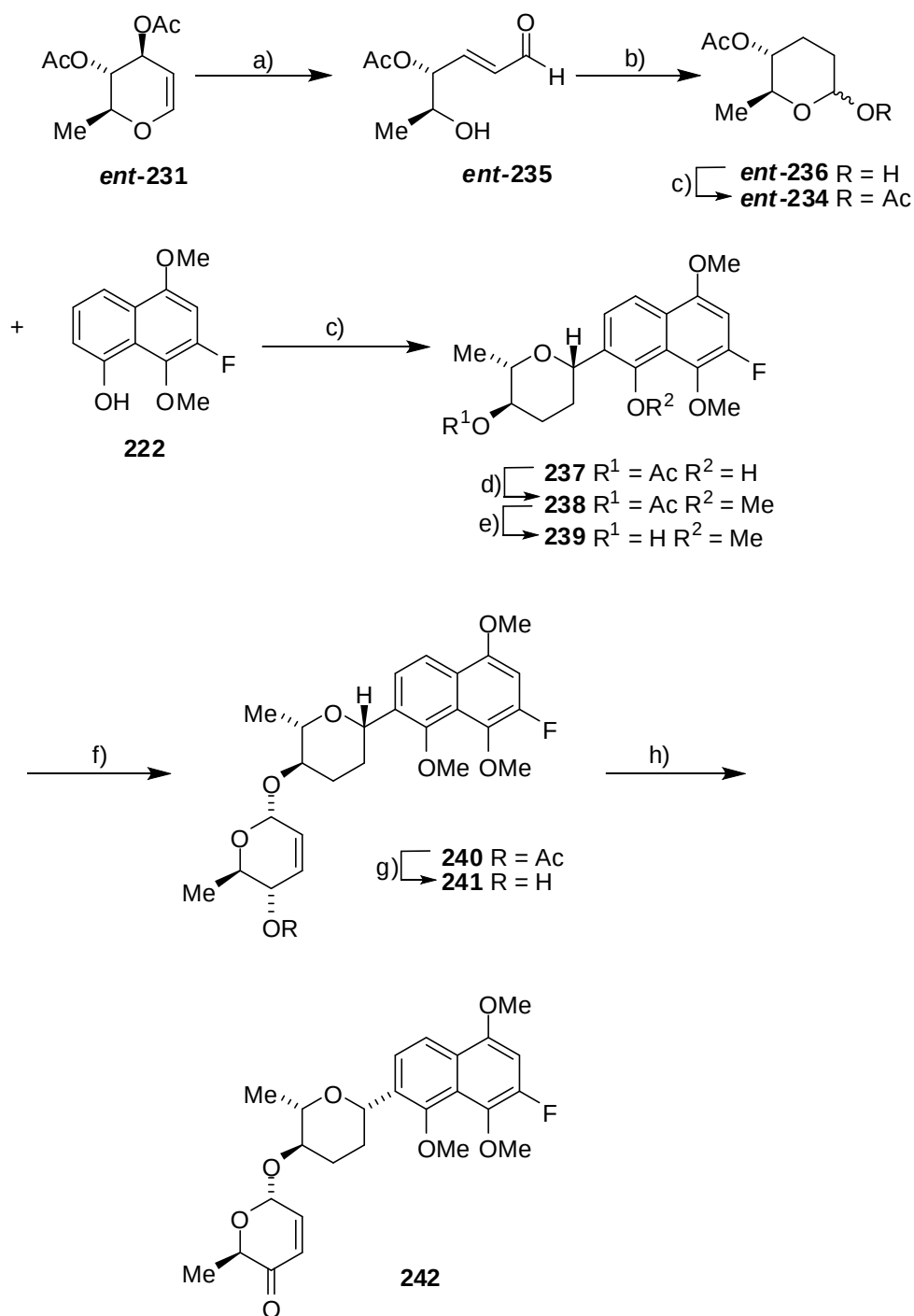
Therefore a new route was devised whereby the glycoside is added *via* a C-glycosidation reaction to the pre-formed naphthol structure. The naphthol is formed from the aryl fluoride and furan and the cycloadduct is opened to give the naphthol. A suitable glycosyl donor will then be allowed to react with the naphthol as the glycosyl acceptor to form the key C-glycoside bond. The second glycoside unit can then be attached (Scheme 53). For ease of synthesis it was decided on this model system to use the enantiomers of glycosides **231** and **234** that would be required for the synthesis of Sch 47554 and Sch 47555.



Scheme 53: Retrosynthesis of Target Disaccharide **230**

In order to synthesise the necessary glycosyl donor **ent-234**, acetate **231** was heated in water at 80 °C to provide the linear *trans*-alkene **235**,¹³⁰ which was hydrogenated at ambient pressure, to provide lactol **ent-236**, the hydroxyl group of which was acetylated, to provide acetate **ent-234**. This was attached to naphthol **222** by treating the substrates with catalytic scandium triflate¹⁰¹ or excess hafnocene dichloride with silver perchlorate⁹⁵ to give the desired C-aryl glycoside, **237**, as a single diastereomer, in 44% or 59% respectively. O-Methylation and saponification gave alcohol **239**.

A Ferrier-type rearrangement of acetate **ent-231**, with alcohol **239** in the presence of indium trichloride¹³¹ gave acetate **240**. This was hydrolysed with potassium carbonate, and oxidised immediately with manganese dioxide to deliver enone **242** (Scheme 54). The synthesis of model disaccharide **242** and its applicability in the total synthesis of Sch 47554 (**1**) and 47555 (**2**) has been published in *Organic Letters*.¹³²



Reagents and conditions: a) H_2O , 80°C , 98%; b) H_2 , Pd/C, EtOH, 75%; c) Ac_2O , $\text{C}_5\text{H}_5\text{N}$, CH_2Cl_2 , 85%; d) $\text{Sc}(\text{OTf})_3$, CH_2Cl_2 , -30°C to rt, 49% or Cp_2HfCl_2 , AgClO_4 , CH_2Cl_2 , -78°C to 23°C , 59%; e) MeI, NaH, DMF, 96%; f) K_2CO_3 , MeOH, 92%; *ent-231*, InCl_3 , CH_2Cl_2 , 78%; g) K_2CO_3 , MeOH; h) MnO_2 , CH_2Cl_2 , 69% over 2 steps.

Scheme 54: The Synthesis of Model Disaccharide **242**

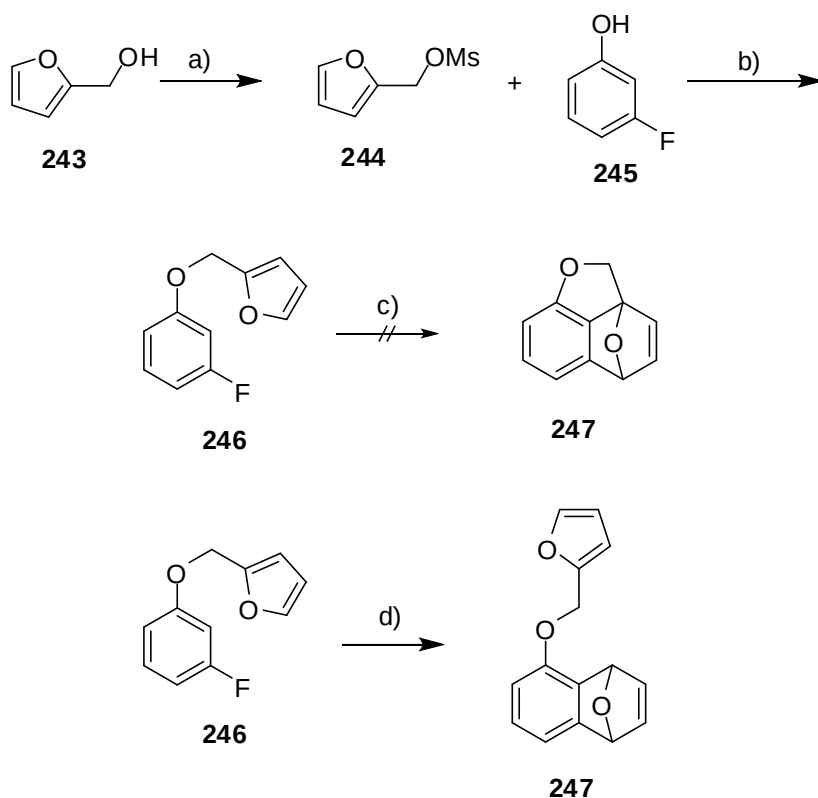
This model system is valuable for determining the methodology to append the glycosidic units to the aglycone, however the work has two major limitations. Firstly, the enantiomers of the appropriate glycosides were used due to the commercial availability of *ent*-**231**. The requisite enantiomer is not commercially available and must be synthesised. The other, more important, issue is that converting the naphthalene unit into something which will be able to further the synthesis will be very difficult and a differing synthetic route to an alternative naphthol will probably be required.

4.2.3 Studies into The Intramolecular Benzyne-Furan Diels-Alder Reaction

Additional work previously carried out in the group concerns the intramolecular benzyne-furan Diels-Alder reaction, brought about by the tethering of the furan moiety to the benzyne precursor.

With regard to the original retrosynthesis, the intention was to have the aryl fluoride and the furan linked by the most practical type of tether system. Therefore, a simple model system was devised and synthesised to give furan **246** (Scheme 55). However, the intramolecular reaction did not succeed, probably because the tether was too short and the substrate could not arrange itself in the necessary conformation to enable the cycloaddition.

In order to confirm that the benzyne was being formed, an intermolecular reaction was attempted, whereby an excess of furan (to ensure complete aryne capture) was present in the reaction mixture. This resulted in the successful formation of cycloadduct **247**, in modest yield.

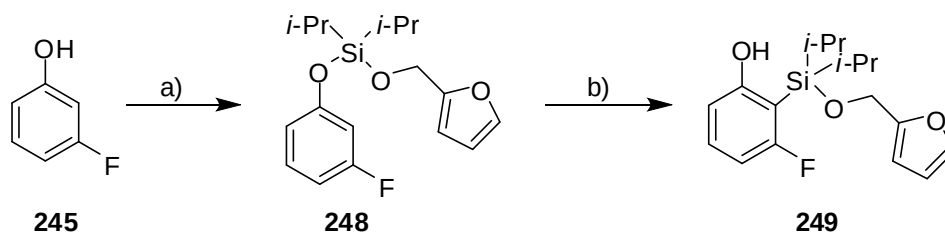


Reagents and conditions: a) MsCl, CH₂Cl₂, NEt₃, 0 °C, b) NaH, DMF, CH₂Cl₂, 85%, 2 steps; c) *n*-BuLi, THF, -78 to 0 °C; d) *s*-BuLi, THF, -78 to 0 °C, furan, 35%

Scheme 55: Preliminary Attempt at the Benzyne-Furan Intramolecular Cycloaddition

Therefore, it was hypothesised that additional atoms must be involved in the tethering. The two moieties need to be attached to the linker *via* oxygen atoms as oxygen functionality is present in the target molecules, but the linker itself can be anything that is synthetically viable, stable and can be removed easily.

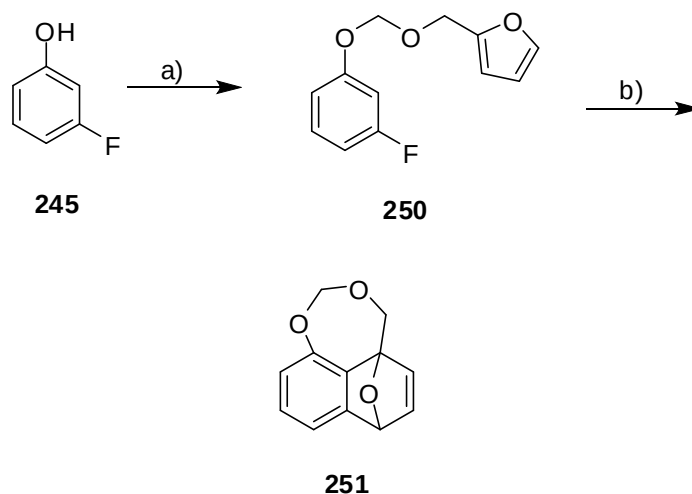
Inspired by the work of Martin *et al.*¹²³ (Scheme 27), silicon-based linkers were first investigated. In Martin's work, the silicon centre is bonded directly to the furan, which is not desired here. Various types of linker were investigated without reward until the di-*iso*-propylsilyl linker was examined, which was synthesised successfully. However, when the cycloaddition reaction was attempted no desired product was observed, due to the more rapid migration of silicon from oxygen to carbon compared to the elimination of lithium fluoride to form the benzyne, resulting in phenol **249** being the only product of the reaction (Scheme 56).



Reagents and conditions: a) furfuryl alcohol, $\text{Cl}_2\text{Si}(\text{i-Pr})_2$, DMAP, NEt_3 , CH_2Cl_2 , 60%; b) LTMP, THF, $-78\text{ }^\circ\text{C}$ to rt

Scheme 56: Synthesis of Silaketal **248** and its Base-Induced Rearrangement

Carbon-based linkers were then investigated, and after a wide screening process, the methoxymethyl ether-type tether was found to be synthetically viable, and on treatment with the cycloaddition reaction conditions, gave the desired product, albeit in a very modest yield of 29% (Scheme 39).



Reagents and conditions: a) furfuryl alcohol, ClCH_2I , NaH, DMF, 51%, b) $n\text{-BuLi}$, THF $-78\text{ }^\circ\text{C}$ to rt, 29%.

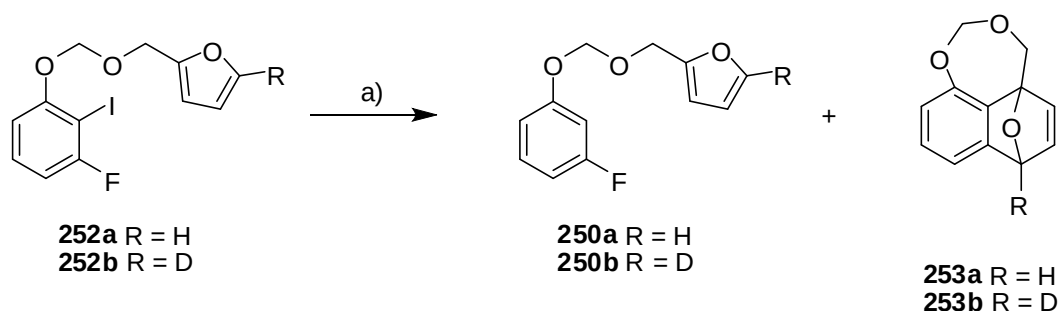
Scheme 57: The Intramolecular Diels-Alder Reaction on Model System **250**

As before, the formation of the aryne was checked by attempting an intermolecular Diels-Alder reaction, using an excess of furan, and the cycloadduct resulting from the intermolecular Diels-Alder reaction was formed in 72%, so it is clear that aryne formation was not problematic, but that it is the inability of the aryne generated to

undergo cycloaddition with the intermolecular furan moiety that hinders the overall reaction.

The generation of the aryne intermediate was next attempted by initial halogen-lithium exchange, and the *ortho*-iodofluoride equivalent, **252a** was investigated in the same reaction but under these conditions, the major product was the deiodinated substrate **250a** and less than 10% of the desired cycloadduct.

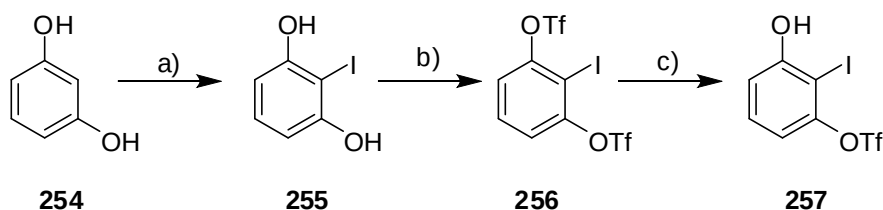
However, after screening a variety of conditions, where the solvent and base were varied, and a 2-deuterated version of the furan, **252b** was used, the reaction was optimised using a modified version of the methodology of Knochel *et al.*⁷⁷ where isopropylmagnesium chloride was allowed to react with the aryl iodides **252a** and **252b** in diethyl ether and **253a** and **253b** were synthesised in 19 % or 51% yield, respectively (Scheme 58).



Reagents and conditions: a) i) *i*-PrMgCl, Et₂O, -78 °C to rt.

Scheme 58: Optimised Procedure for Generation of Cycloadducts **253a** and **253b**

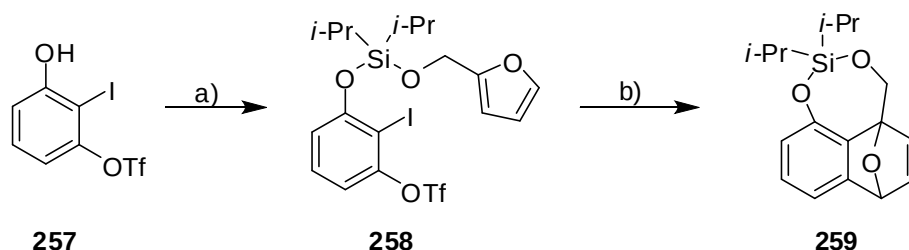
The limiting factor in this reaction was now thought to be the relatively poor leaving ability of the fluorine, so this functionality was now altered, and the equivalent aryl triflate moiety was investigated. The desired aryl triflate was synthesised successfully by Suzuki's procedure,¹³³ where resorcinol was iodinated, *bis*-triflated and a single triflate cleaved to deliver phenol **257** (Scheme 59).



Reagents and conditions: a) I_2 , NaHCO_3 , H_2O , $0\text{ }^\circ\text{C}$ to rt, 62%; b) Tf_2O , $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$ to rt, 99%; c) Cs_2CO_3 , DME, $80\text{ }^\circ\text{C}$, 92%.

Scheme 59: Synthesis of Phenol 257

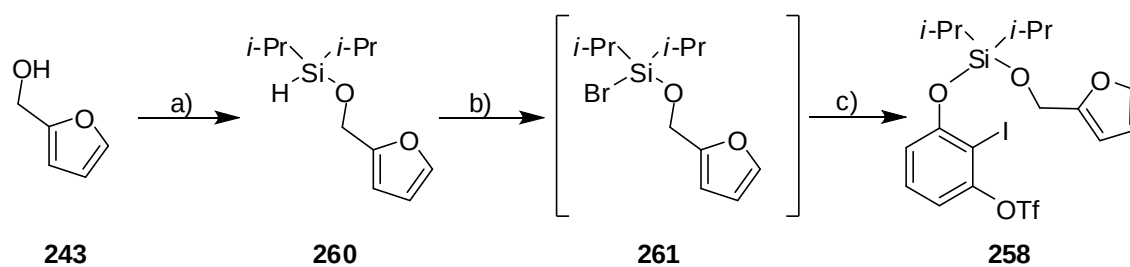
The methoxymethyl tether that was used with the iodo-fluoride aryne precursor was unsuccessful in the iodo-triflate series, however, it was discovered that the silicon-based tethers, unsuccessful in the iodo-fluoride series, did work here, and so the silaketal **258** was synthesised (Scheme 60), and when *iso*-propylmagnesium chloride was used to generate the aryne, the cycloadduct **259** was formed in an improved yield of 70%.



Reagents and conditions: a) furfuryl alcohol, $\text{Cl}_2\text{Si}(i\text{-Pr})_2$, DMAP, Et_3N , CH_2Cl_2 , 35%; b) $i\text{-PrMgCl}$, Et_2O , $-78\text{ }^\circ\text{C}$ to rt

Scheme 60: Iodo-triflate-Derived Aryne-Furan Intramolecular Reaction

The formation of silaketal **258** was modest, 35%, and therefore an improved method for this key transformation was sought. A one-pot synthesis of unsymmetrical silaketals is reported¹³⁴ (Scheme 61), but using these conditions, synthesis of the desired product was not successful. However, when the transformation was conducted in a stepwise manner, with isolation and purification of the intermediate silane **260**, it was successful in 43% overall yield.



Reagents and conditions: a) $\text{Cl(H)Si}(i\text{-Pr})_2$, DMAP, Et_3N , CH_2Cl_2 , 68%; b) NBS, CH_2Cl_2 ; c) **257**, DMAP, Et_3N , 63%

Scheme 61: Alternative Synthesis of Silaketal **258**

This summary has shown that the previous work in the group has initiated the synthesis of Sch 47554 and made considerable progress, using extensive model studies to optimise methodology that it is envisaged will be used in the synthesis of this natural product.

4.3 Updated Project Objective

The overall objective is the completion of the synthesis of Sch 47554 and 47555, and the results gained previously are a base from which to develop and conclude these syntheses. The studies into the intramolecular Diels-Alder reaction, discussed previously, are the primary area of focus, as there is still much that can be undertaken in this area. The first targets are the three molecules **259**, **260** and **261** (Figure 7) which are much more realistic model systems for studying the intramolecular benzyne-furan Diels-Alder reaction, both in the iodotriflate series, and the iodofluoride series.

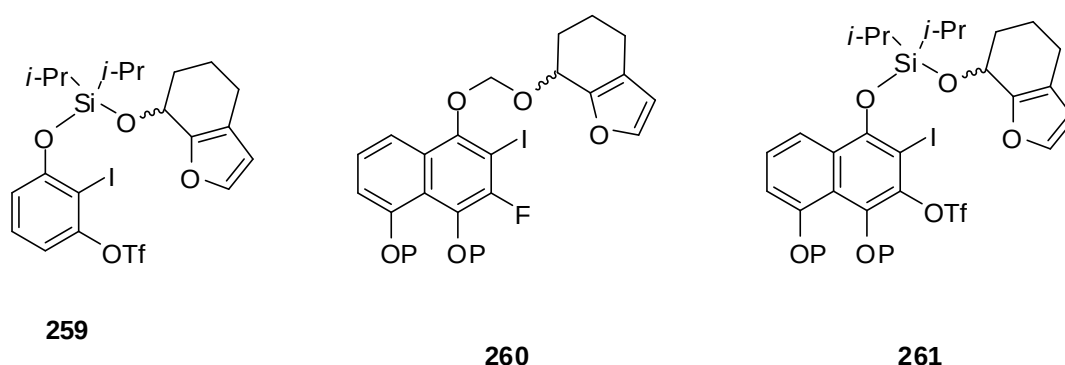
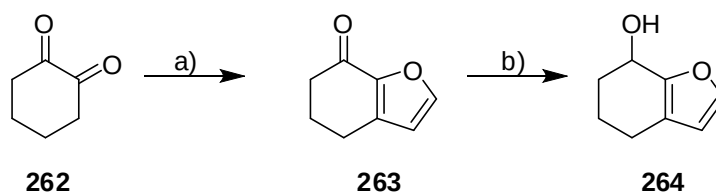


Figure 7: Model Systems for the Study of the Intramolecular Diels-Alder Reaction

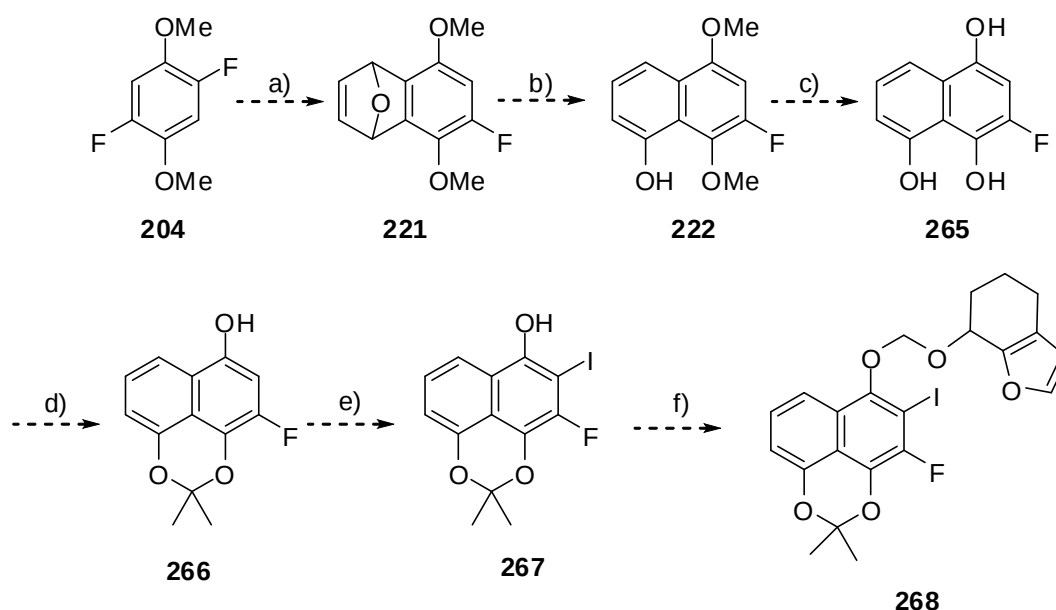
These molecules all possess a tetrahydrobenzofuranol-derived moiety for the furan aspect of the molecule. This was not utilised significantly before, as commercially available furfuryl alcohol was preferred and the required alcohol **264** is only available via a low-yielding two-step synthesis¹³⁵ from cyclohexane-1,2-dione (Scheme 44).



Reagents and conditions: a) i) chloroacetaldehyde, NaHCO_3 , H_2O , 0 °C to rt, ii) H_2SO_4 , 41%; b) LiAlH_4 , THF, 0 °C, 63%.

Scheme 62: Synthesis of Tetrahydrobenzofuranol **264**

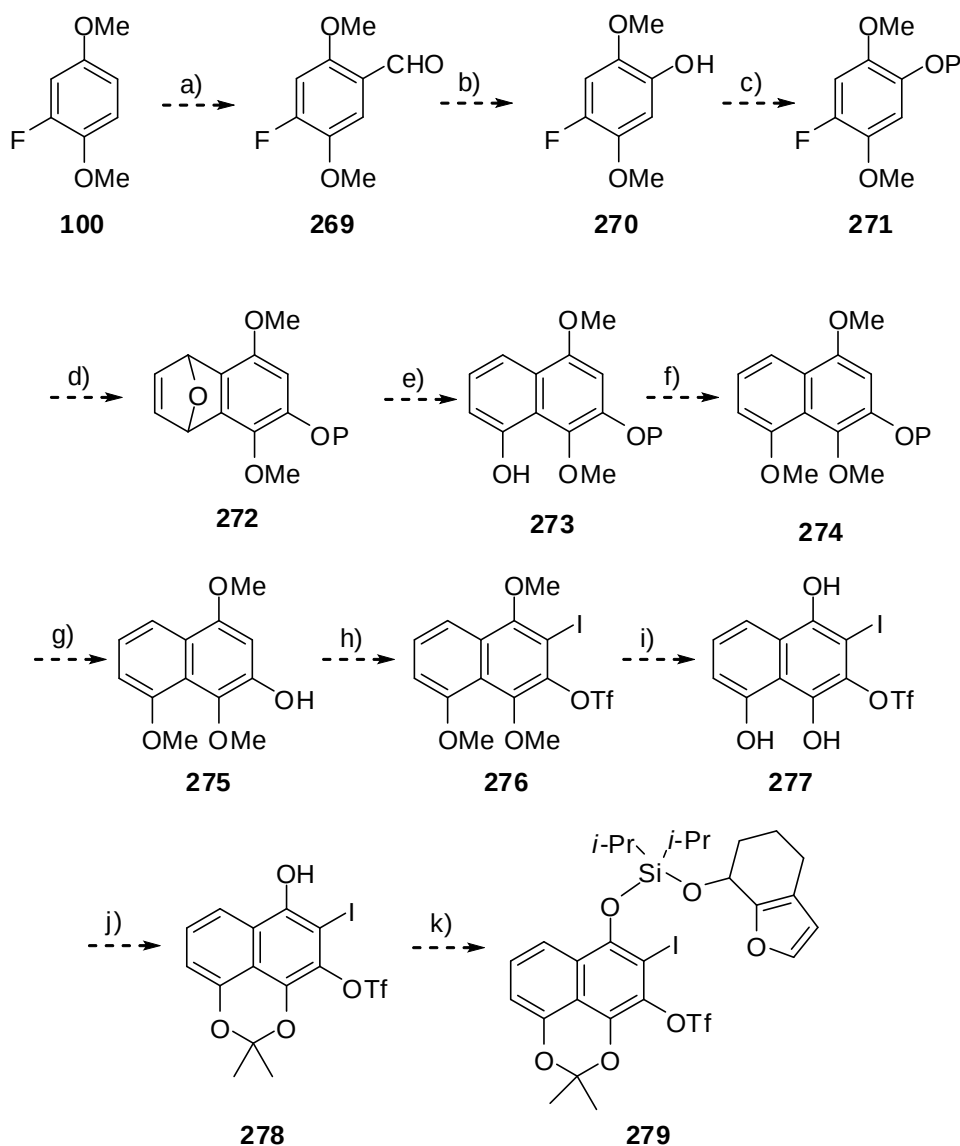
The synthesis of the naphthalene-based aryne precursors are necessarily more complicated. The envisaged route to **263** is shown in Scheme 63. As already demonstrated in the group, **204** can be lithiated, and upon warming in the presence of furan, can form cycloadduct **221**, which can be aromatised in acidic conditions.¹²⁹ The resulting naphthol should then be able to be demethylated, forming the triol, and then selectively reprotected as an isopropylidene acetal to give the naphthol **266**. This can then be iodinated *ortho* to the phenol, giving the relevant iodo-fluoride aryne precursor. This iodo-fluoride can then be tethered to the furan using the previously developed conditions, to give the Diels-Alder precursor **268**.



Reagents and conditions: a) i) *n*-BuLi, THF, -78 °C, ii) furan, -78 °C to rt; b) 6 M HCl, MeOH, Δ; c) BBr₃, CH₂Cl₂; d) acetone, H⁺; e) base, I₂; f) base, ClCH₂I, **264**

Scheme 63: The Planned Synthesis of Aryl Fluoride **268**

The synthesis of iodotriflate **279** is also more complicated. Formylation of 2,5-dimethoxyfluorobenzene gives exclusively benzaldehyde **269**,¹³⁶ followed Dakin oxidation, which should deliver phenol **270**. This can be protected, before being subject to benzyne formation and cycloaddition with furan to yield **272**, which is then aromatised with similar regioselectivity as described previously. Naphthol **273** can be methylated, and then deprotection of the earlier synthesised hydroxyl functionality enables *ortho*-iodination and triflation. Global demethylation, followed by selective reprotection of the 1,3-alcohols with an isopropylidene acetal delivers naphthol **278**, which can then be tethered to the tetrahydrobenzofuranol moiety with a silicon linker in the standard way to give silaketal **279** (Scheme 64).



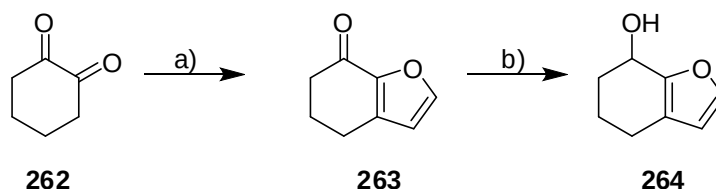
Reagents and conditions: a) i) SnCl_4 , Cl_2CHOMe , CH_2Cl_2 , ii) aq. HCl ; b) i) *m*-CPBA, CH_2Cl_2 ii) aq. NaOH ; c) protection; d) i) *n*-BuLi, THF, -78°C , ii) furan, -78°C to rt; e) aq. HCl , MeOH, Δ ; f) NaH, MeI, DMF; g) deprotection; h) i) base, I_2 ; ii) Tf_2O , base, CH_2Cl_2 ; i) BBr_3 , CH_2Cl_2 ; j) acetone, H^+ , k) NEt_3 , DMAP, **189**.

Scheme 64: The Proposed Synthesis of Silaketal **279**

Chapter 5: Results and Discussion – Studies Towards Model Systems for Aryne-Furan Cycloaddition Precursors

5.1 Synthesis of Furanol 264

The synthesis of the more accurate model furan **264** was undertaken. The procedure is a two-step process, involving a modified Feist-Bénary furan synthesis on 1,2-diketone **262** with chloroacetaldehyde, followed by reduction of the remaining ketone functionality of the benzofuranol product **263**, using lithium aluminium hydride (Scheme 65).¹³⁵ This yields the desired tetrahydrobenzofuran, **264**.



Reagents and Conditions: a) i) 40% aq. chloroacetaldehyde, NaHCO₃, H₂O, 0 °C to rt, ii) H₂SO₄, 39%; b) LiAlH₄, THF, 0 °C, 53%.

Scheme 65: The Synthesis of Furan **264**

This route suffers from low yields; 21% over two steps. The base in the initial furan synthesis was varied in order to determine if this was the cause for the number of side products observed (Table 2).

Entry	Base Used	Temperature (/ °C)	Yield (/ %)
1	NaHCO ₃	23	39
2	Na ₂ CO ₃	23	15
3	NaOH	23	25
4	NEt ₃	23	18
5	Pyridine	23	17
6	Pyridine	50	10 (impure)

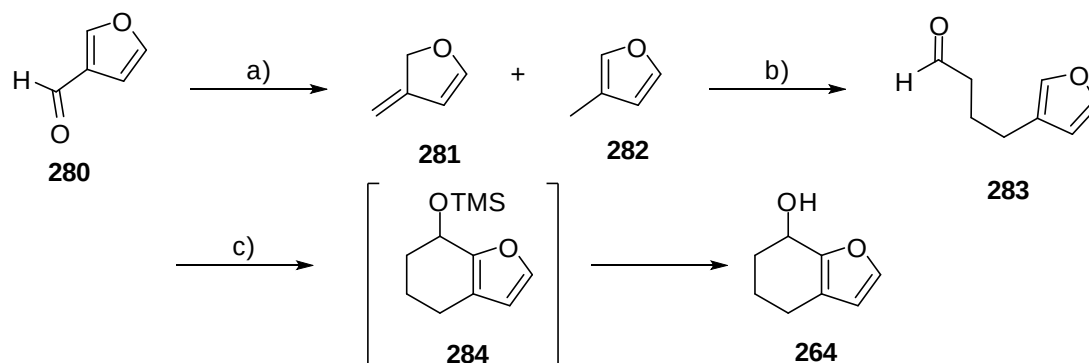
Table 2: The Effect of Different Bases on the Synthesis of Furanone **263**

It was concluded that the reaction was most reliable with sodium hydrogen carbonate, as stronger inorganic bases and nitrogen bases gave poorer yields. The order of addition of components was also varied, but this had no positive effect on the yield.

A second route to furanol **264** was thus investigated, using the methodology of Miles *et al.*,¹³⁷ in which an intramolecular cyclisation of a carbonyl moiety onto a furan, analogous to a Friedel-Crafts reaction, is the key step. Using an aldehyde and silyl triflate the corresponding silyl ether is formed. Aldehyde **283** can be made from an ene reaction between acrolein and 3-methylene-2,3-dihydrofuran **281**, itself synthesised by a Huang-Minlon modified Wolff-Kishner reduction of furaldehyde **280**.¹³⁸

This procedure was undertaken and the Wolff-Kishner reduction of aldehyde **280** was successful, dihydrofuran **281** and undesired furan **282** were distilled directly from the reaction and this mixture (2.7:1 in favour of the desired dihydrofuran) was used immediately in the next step due to the extreme acid-sensitivity of dihydrofuran **281** (it was found that even the trace acid present in chloroform will tautomerise it to **282** in two hours). The Alder ene reaction with acrolein was successful and at this stage the product could be purified.

The cyclisation was then undertaken, not with *tert*-butyldimethylsilyl triflate, but trimethylsilyl triflate, in order that an acidic work-up would render the desired furanol **264**. In the event, this strategy proved viable and **264** was accordingly obtained (Scheme 66).



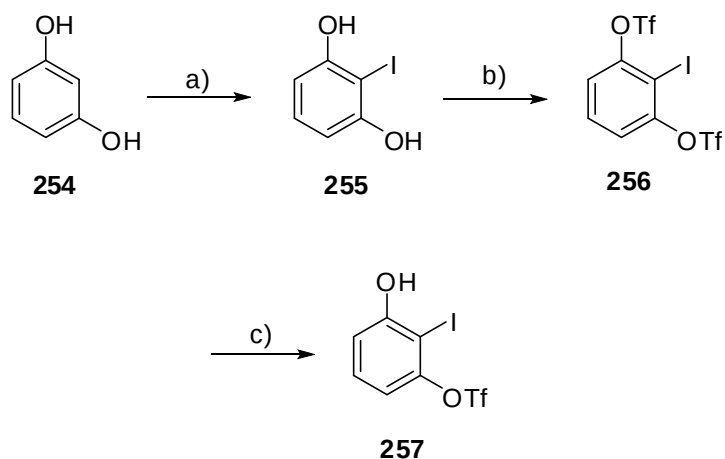
Reagents and Conditions: a) i) $\text{H}_2\text{N-NH}_2$, ethylene glycol, ii) KOH, 150 °C, 74% (**281** and **282**, 2.7 : 1 ratio, effective yield of **281** 54%); b) $\text{H}_2\text{C=CHCHO}$, CH_2Cl_2 , Δ , 73%; c) TMS-OTf, CH_2Cl_2 , 0 °C to rt, 68%

Scheme 66: An Alternative Synthesis of Furanol **264**

In this case, furanol **264** was obtained in 27% overall yield which was a small improvement, but had the synthetic advantage of obviating the need for lithium aluminium hydride and the difficult purification of furanone **263**.

5.2 Synthesis of Model Benzyne Precursor **257**

The simple benzene-derived model aryne precursor can be synthesised using a known procedure¹³³ (Scheme 67), as described previously. Selective iodination, followed by double triflation and selective mono-hydrolysis led to the desired phenol **257** in 56% yield over three steps from resorcinol.



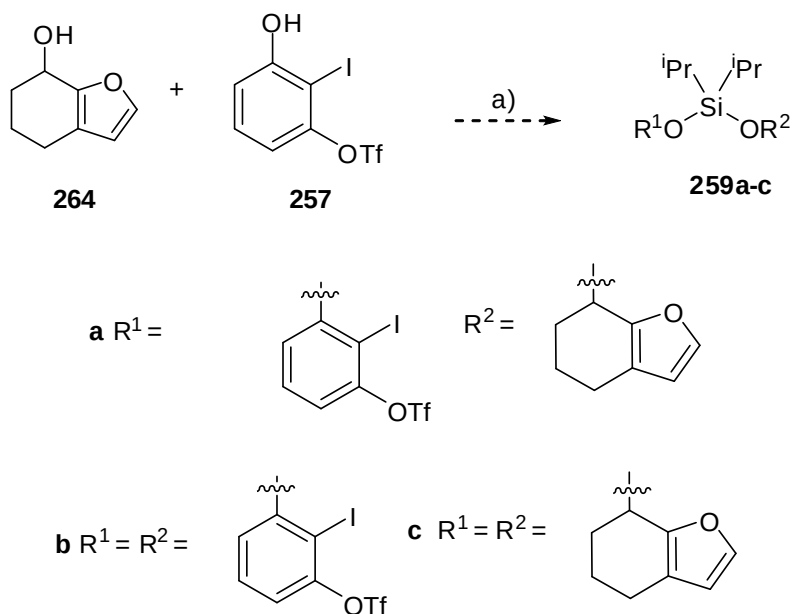
Reagents and conditions: a) NaHCO_3 , I_2 , H_2O , 71%; b) Tf_2O , $(i\text{-Pr})_2\text{NEt}$, CH_2Cl_2 , 94%; c) Cs_2CO_3 , DME, 80°C , 84%

Scheme 67: Synthesis of Phenol **257**

5.3 Synthesis of Silaketals Used As Tethers

With phenol **257** and iodotriflate **264** in hand, attempts could be made to investigate the silicon linkers that could be used to tether the cycloaddition reaction and make it intramolecular, controlling the regioselectivity in the process.

Previous work in the group has shown that it is possible to synthesise such unsymmetrical silaketals, albeit in fairly low yields, simply by using the two relevant alcohols, a suitable base and dichlorodi-*iso*-propylsilane. Therefore, this methodology was attempted with phenol **257** and alcohol **264** (Scheme 68).

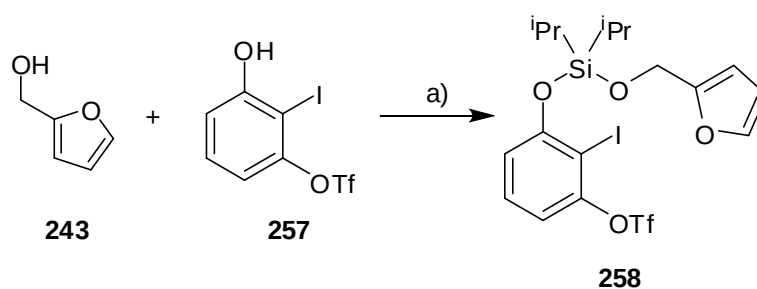


Reagents and conditions: a) NEt_3 , DMAP, $\text{Cl}_2\text{Si}(\text{i-Pr})_2$, CH_2Cl_2

Scheme 68: Procedure for the Synthesis of Unsymmetrical Silaketals

This reaction was undertaken, but ^1H NMR and TLC indicated that, as expected, the resulting reaction mixture contained several different compounds. Chromatography enabled the separation of a UV-active species, however ^1H NMR indicated that it was not one compound but consisted of multiple species. The desired product, silaketal **259a**, could be tentatively assigned as a component, however the other components, the symmetrical silaketals **259b** and **259c**, were observed as co-eluting products which made unambiguous assignment and yield determination impossible. In any case, the reaction seems unlikely to be useful in providing **259a** in any meaningful amount even were it isolable. All attempts at sequential addition of the alcohols or adding the dichlorosilane to solutions pre-mixed with base were unsuccessful in improving the yield or isolation of the desired silaketal **259a**.

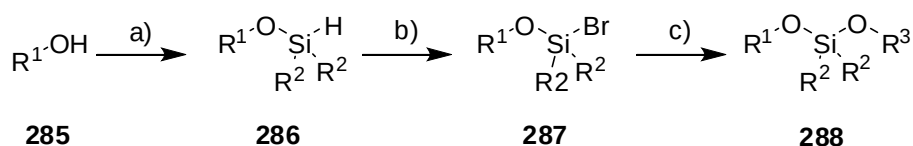
The reaction was repeated using the simpler furan, commercially available furfuryl alcohol **243** which has been previously demonstrated to afford the desired silaketal (Section 4.2.3).¹³⁹ This time, the reaction was more successful, giving only two main products that were chromatographically separable, one of which was the desired silaketal **258** (the other product being the inconsequential double furanol silaketal) indicating that the viability of this reaction depends on the furanol used (Scheme 69).



Reagents and conditions: a) NEt₃, DMAP, Cl₂Si(*i*-Pr)₂, CH₂Cl₂, 34%

Scheme 69: Procedure for the Synthesis of Unsymmetrical Silaketals with Furfuryl Alcohol

Malacria *et al.* report the improved synthesis of unsymmetrical silaketals in a one-pot procedure that consists of reaction of the first alcohol with a chlorodialkylsilane, subsequent bromination at silicon, and displacement of the bromine with the second alcohol (Scheme 70).¹⁴⁰



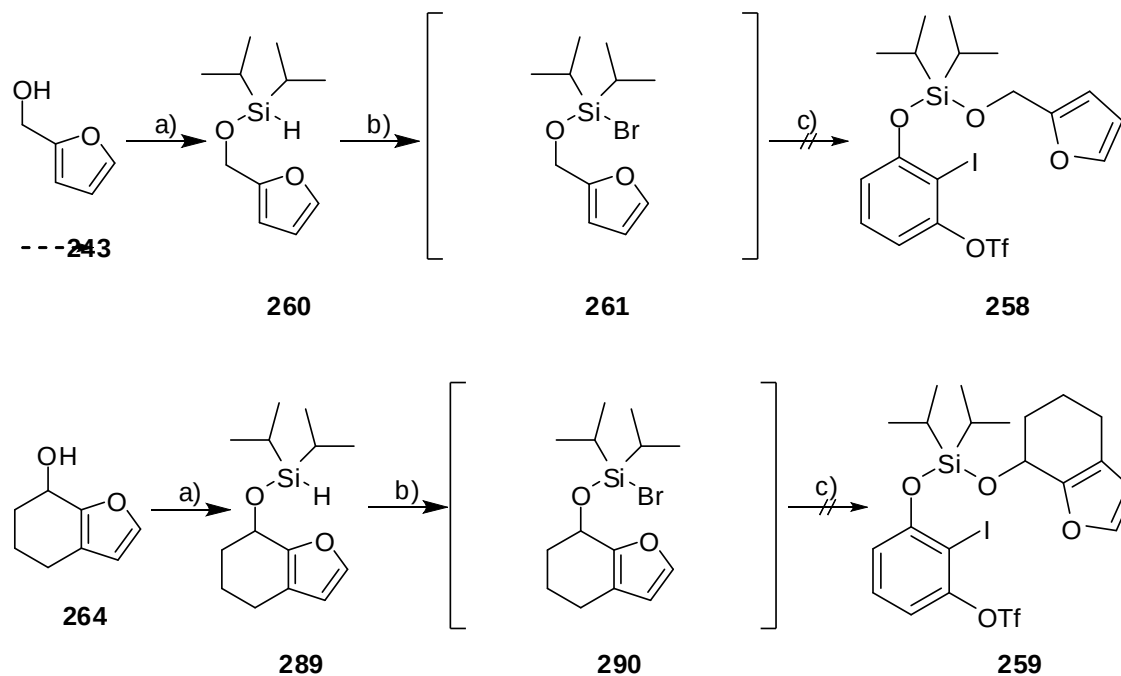
Reagents and conditions: a) (R²)₂Si(H)Cl, base; b) NBS; c) R₃OH, base

Scheme 70: Alternative Procedure for the Synthesis of Unsymmetrical Ketals

This methodology was attempted in previous research within the group using **264** and **257** as the alcoholic components, but was found to be unsuccessful. However, if the intermediate after the first silylation was isolated and then the subsequent reaction protocol applied to this substrate after purification, the silaketal **258** could be successfully synthesised, albeit in a low yield (Scheme 71).

The methodology was applied to furan **264** and the resulting silane **260** was synthesised without incident in high purity, however the bromination step yielded a complex mixture of products and was not as clean as described. After several attempts to vary the conditions and to quench the silyl bromide with different alcohols, this

route was temporarily abandoned, but was then investigated further elsewhere in the group with different methodology utilising palladium to chlorinate the silane. The results will be detailed in Section 6.2.

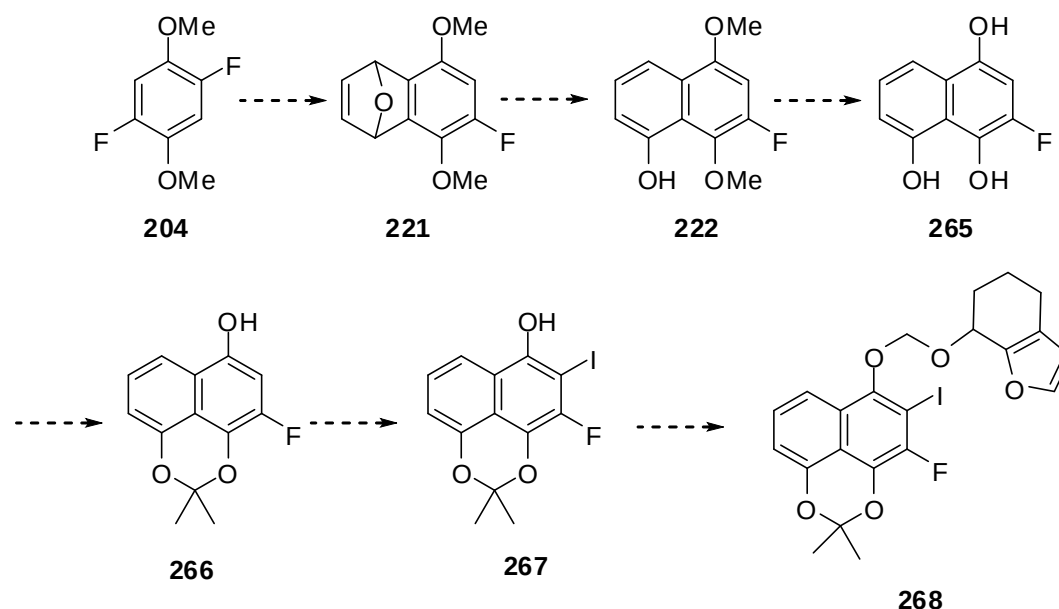


Reagents and conditions: a) NEt_3 , DMAP, chlorodiisopropylsilane, CH_2Cl_2 ; b) NBS, CH_2Cl_2 , c) **257**, NEt_3 , DMAP

Scheme 71: Alternative Synthesis of Unsymmetrical Silaketals

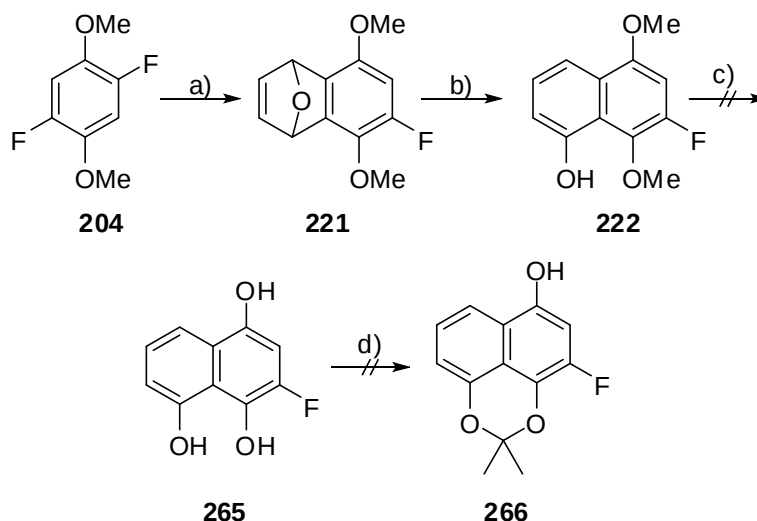
5.4 Towards the Synthesis of Iodofluoride 268

The second aryne precursor that will be examined in the intramolecular aryne-furan Diels-Alder reaction is the iodofluoride **268**. The planned route is shown in Scheme 72.



Scheme 72: Planned Synthesis of Fluoride **268**

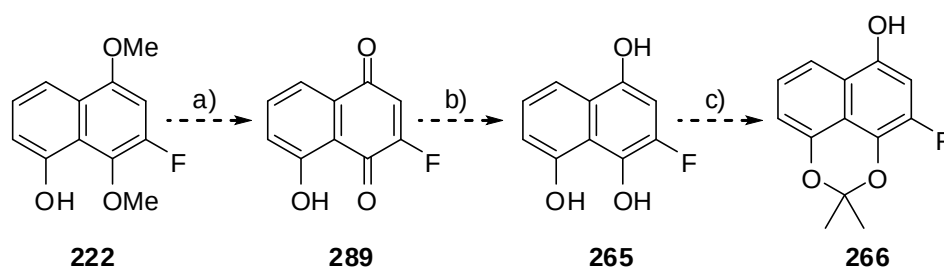
The conversion of aryl fluoride **204** to the cycloadduct **221**, and the acid-catalysed aromatisation to naphthol **222** have been previously described in the group,¹²⁹ as outlined in Section 4.2.1. Consequently, fluoride **204** was lithiated at $-78\text{ }^{\circ}\text{C}$ and, upon warming to ambient temperature, formed the aryne, and the desired cycloaddition reaction with furan was achieved, the resultant cycloadduct **221** was isolated in 82% yield and was subsequently aromatised under the established acidic conditions in 85% yield with the exclusive regioselectivity described in Section 4.2.1. The next step was demethylation to obtain the triol **265**, which was attempted with boron tribromide in dichloromethane, but isolation of the triol proved unsuccessful. The reaction was repeated with the acetalisation undertaken without isolation of the triol intermediate, using methanol to open the boron ester, in order to keep the reaction anhydrous, however this similarly resulted in a lack of any desired product, neither the triol **265** nor the acetal **266** (Scheme 73).



Reagents and conditions a) i) *n*-BuLi, THF, $-78\text{ }^{\circ}\text{C}$; ii) furan, $-78\text{ }^{\circ}\text{C}$ to rt, 74%; b) 6M HCl, MeOH, Δ , 76%; c) BBr₃, CH₂Cl₂; d) acetone, H₂SO₄

Scheme 73: Attempted Synthesis of Naphthol **266**

Alternatives to this procedure thus had to be sought. Another method of removing methyl ethers from aromatic systems such as **222** is to oxidise the ring to a quinone with ceric ammonium nitrate (CAN). This can then be reduced back down to the hydroquinone system with sodium dithionite to generate, in this case, the triol **265**. This is detailed in Scheme 74.

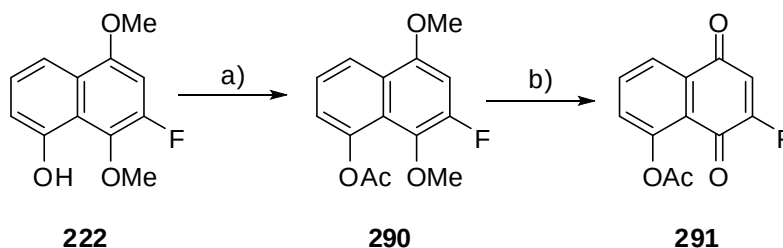


Reagents and conditions a) aq. CAN, MeCN, $0\text{ }^{\circ}\text{C}$; b) aq. Na₂S₂O₄ in Me₂CO; c) Me₂CO, H₂SO₄

Scheme 74: Alternative Route to Acetal **266** via Quinone **289**

Unfortunately the oxidation of **222** did not occur in the desired manner and the only product was the quinone formed by oxidation of the hydroxyl-bearing ring, leaving the methoxy groups intact. Therefore, the free alcohol must be protected with something that can deactivate the second ring, and so **222** was acetylated with acetic anhydride in pyridine, to yield ester **290** in 87% yield. This was then submitted to the

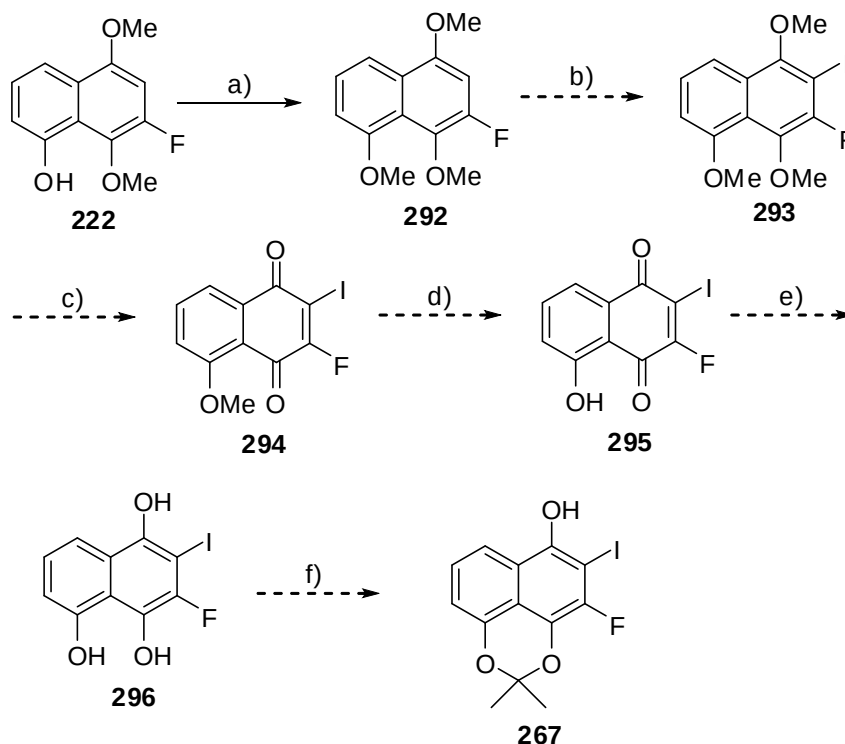
oxidation conditions, and this time the desired ring was oxidised to yield quinone **291** (Scheme 75).



Reagents and conditions a) Ac_2O , DMAP, pyridine, 87%; b) aq. CAN, MeCN, 0 °C, 82%

Scheme 75: Successful Oxidation of Acetate 290

A potential problem with the route *via* **266** is that the iodine will prove difficult to attach at the end of the synthesis, or will only deliver the iodide in modest yields. To ensure the most rewarding route is being utilised, an early-stage iodination route was simultaneously being explored, whereby the iodine is attached before this oxidation step. A synthetic sequence involving methylation of naphthol **222**, lithiation with *n*-butyllithium and iodine quenching is envisaged to yield iodide **292**, as the fluoride substituent should direct lithiation exclusively *ortho* to itself. This can then be oxidised to the quinone, demethylated to the juglone **295**, and then reduced and protected as the acetal **267** (Scheme 76). If the demethylation proves difficult, the naphthol can be acetylated, as demonstrated above.



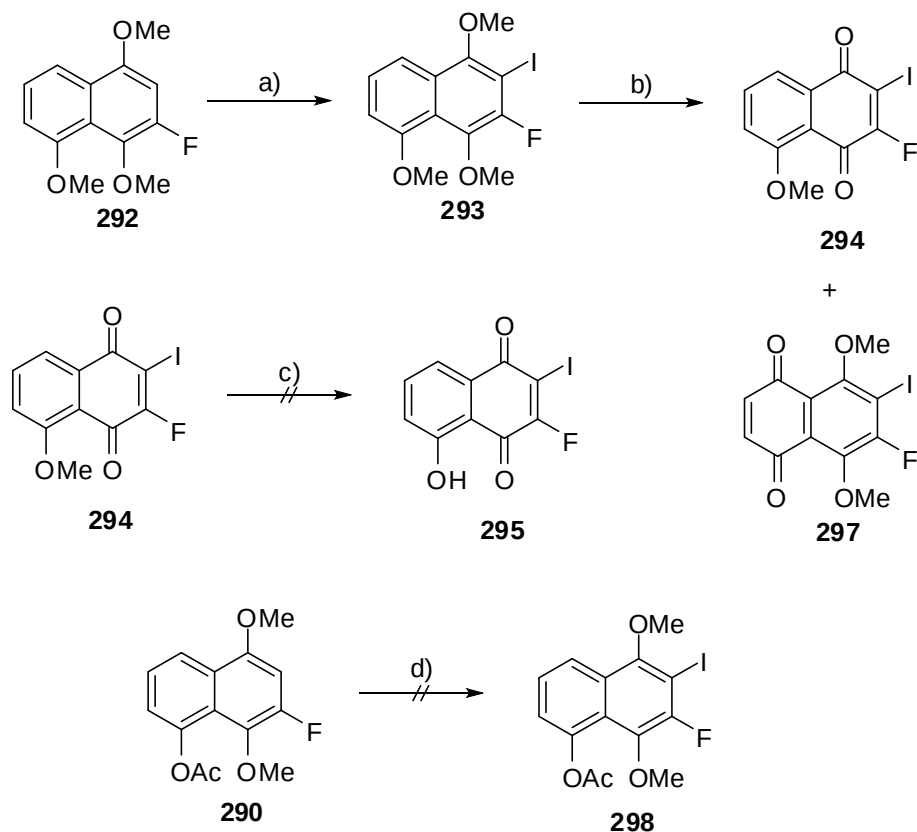
Reagents and conditions a) NaH, MeI, DMF; b) i) *n*-BuLi, THF, -78°C , ii) I_2 ; c) aq. CAN, MeCN, 0°C ; d) BBr_3 , CH_2Cl_2 , 0°C ; e) aq. $\text{Na}_2\text{S}_2\text{O}_4$ in Me_2CO ; f) Me_2CO , H_2SO_4

Scheme 76: Modified Route to Acetal **267**

The methylation proceeded without incident under standard conditions (sodium hydride, methyl iodide, 90%) and the lithiation and iodine quench also proved uncomplicated and regioselective due to the reinforced *ortho*-directing abilities of the methoxy and fluoride substituents, yielding aryl iodide **293** in 84% yield. The oxidation with CAN yielded the desired quinone **294** as the major product (85%), with only small amounts of the undesired quinone **297** present (*ca.* 5%).

However, demethylation of **294** using boron tribromide gave no identifiable product. A range of conditions were employed, but in all cases no desired juglone product **295** was obtained.

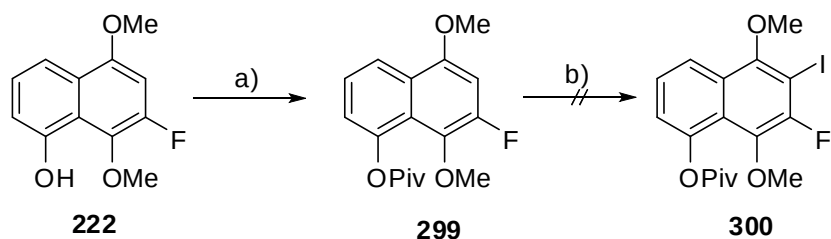
Instead of using a methyl protecting group in this position, iodination of acetate **290** with lithium diisopropylamine (LDA) and iodine quench was also attempted to give the acetate **298**, but this resulted in a tar-like product which also defied identification (Scheme 77).



Reagents and conditions: a) i) *n*-BuLi, THF, - 78 °C ii) I₂, 84%; b) aq. CAN, MeCN, 0 °C, 85%, c) BBr₃, CH₂Cl₂; d) i) LDA, THF, - 78 °C, ii) I₂

Scheme 77: Attempted Iodination of Aryl Fluorides 290 and 294

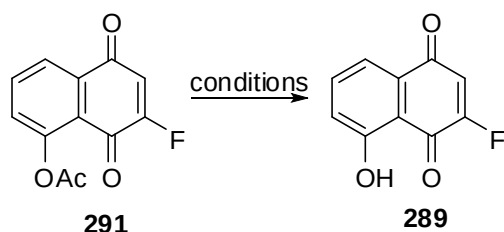
Therefore, a different ester group was examined as it was thought that the acidic protons on the acetyl group were problematic. Thus, the pivaloyl ester was investigated, and ester **299** was synthesised with pivaloyl chloride, DMAP and pyridine in 85% yield. The iodination was then examined on this substrate and although the reaction product was not as complex as the equivalent reaction with the acetyl analogue, the desired product, iodide **300**, was not able to definitively identified and isolated pure.



Reagents and conditions: a) PivCl, DMAP, pyridine, 85%; b) i) LDA, THF, - 78 °C, ii) I₂

Scheme 78: Pivaloylation of Naphthol **222** and Attempted Iodination of Pivalate **299**

Returning to the original route in which the iodine functionality is added later in the synthesis, hydrolysis of the acetate **291** was then required in order to obtain juglone **289** (Scheme 79). Standard acidic conditions for this transformation (dilute hydrochloric acid in refluxing acetone) resulted in surprisingly low conversion, so a range of alternative conditions were explored. These are summarised in Table 3.



Scheme 79: Synthesis of Juglone **291** via Hydrolysis of Acetate **289**

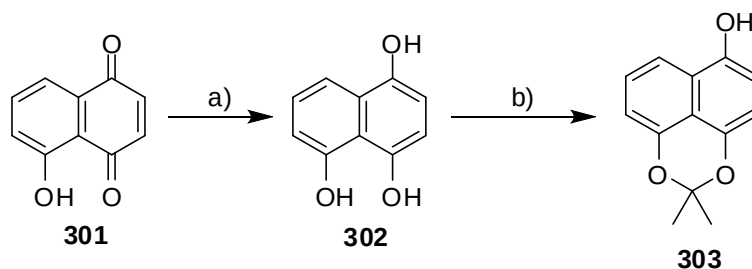
Entry	Reagent	Solvent	Temperature (/ °C)	Time (/ h)	Yield of 289 (/%)
1	HCl	Me ₂ CO	60	1	19
2	HCl	Me ₂ CO	60	4	18
3	H ₂ SO ₄	EtOH	80	2	9
4	K ₂ CO ₃	MeOH	23	5	15
5	BF ₃ ·OEt ₂	CH ₂ Cl ₂	23	15	<10
6	AlCl ₃	CH ₂ Cl ₂	23	1	73

Table 3: Conditions Examined in the Hydrolysis of Acetate **291**

The Brønsted acid-mediated reactions appeared to result in mainly decomposition products, with only small amounts of juglone **289** after purification (Entries 1-3). Basic conditions resulted in one unidentified major product and a small amount of **289** as a side product (Entry 4). The Lewis acids boron trifluoride and aluminium chloride were then tested. The former returned mainly starting material, even after 15 hours, with only trace amounts of **289** (Entry 5), whereas aluminium trichloride effected the hydrolysis cleanly and rapidly at ambient temperature to give **289** in 73% yield (Entry 6).

The reduction of the quinone to the hydroquinone and subsequent acetalisation reaction sequence was first examined using 5-hydroxy-1,4-naphthoquinone (juglone, **301**) instead of **289**, as **301** is commercially available and inexpensive. The first step was the reduction of the quinone to the hydroquinone **302**, which was accomplished with sodium dithionite. The reaction worked best in a biphasic ether/ water solvent system but succeeded in a number of different solvents such as a monophasic acetone/water system (with ether extraction) or an ethyl acetate/water system. The hydroquinone is unstable with respect to the starting material, and can undergo facile aerial oxidation and thus was not analysed or stored, but always used immediately.

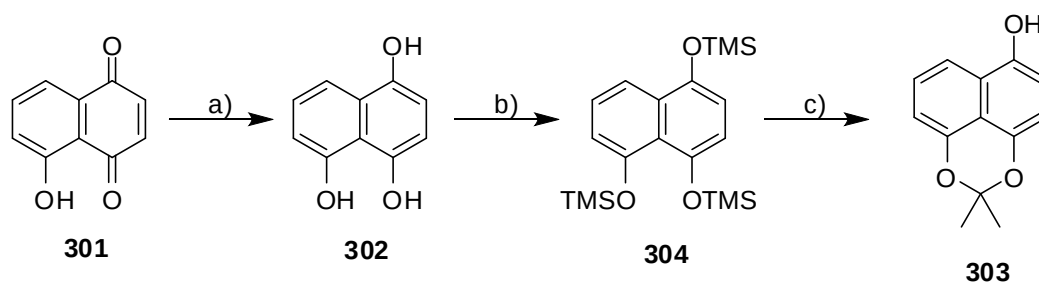
The acetalisation was examined with a variety of acids. Using PTSA and 2,2-dimethoxypropane in acetone, the product was obtained in variable yields, but was consistently impure after chromatography. Using sulfuric acid in acetone gave higher and more consistent yields (55-58%) and the products were notably purer, though still somewhat impure. Using boron trifluoride gave a complex mixture of unidentifiable products (Scheme 80).



Reagents and conditions: a) aq. $\text{Na}_2\text{S}_2\text{O}_4$, Et_2O ; b) conc. H_2SO_4 , Me_2CO or PTSA, Me_2CO or PTSA, 2,2-dimethoxypropane, Me_2CO or $\text{BF}_3 \cdot \text{OEt}_2$, 2,2-dimethoxypropane, Me_2CO .

Scheme 80: Transformation of Juglone **301** into Acetal **303**

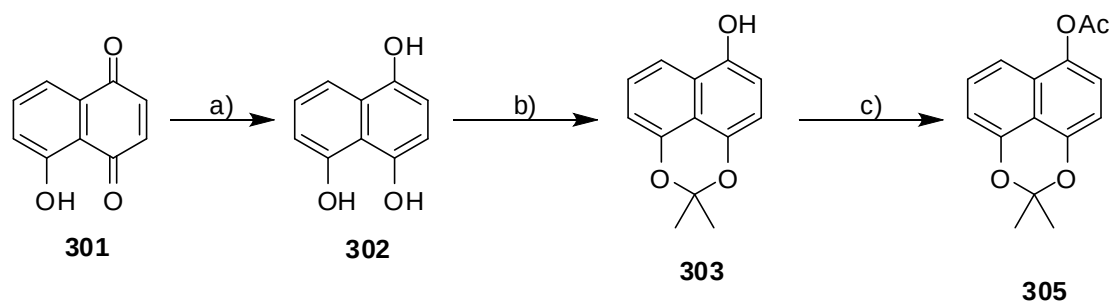
An alternative procedure based on methodology to form acetals by Noyori *et al.*¹⁴¹ was examined, using the trimethylsilyl ether of the hydroxyl functions, and trimethylsilyl triflate as a catalyst. Hydroquinone **302** was generated as before, and then immediately trimethylsilylated. The resulting crude tris(trimethylsilylether) was treated with acetone in the presence of trimethylsilyl triflate in order to obtain acetal **303**. In the preliminary attempt, acetal **303** was isolated in 17% yield after chromatography (Scheme 81).



Reagents and conditions: a) aq. $\text{Na}_2\text{S}_2\text{O}_4$, Et_2O ; b) TMSOTf, NEt_3 , DMAP, CH_2Cl_2 , 0 °C to rt; c) Me_2CO , TMSOTf, CH_2Cl_2 , - 78 °C, 17% (3 steps).

Scheme 81: Alternative Procedure for the Transformation of Juglone **301** into Acetal **303** via Tris(trimethylsilylether) **304**

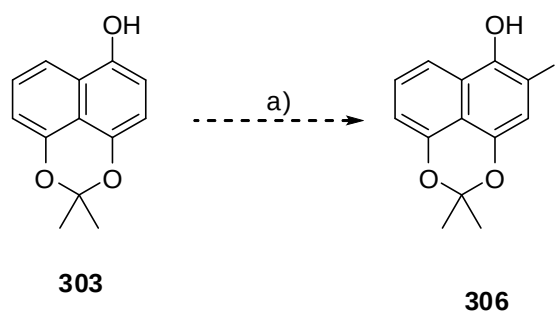
The semi-purified acetal **303** was then subjected to acetylation conditions, in order to try and obtain a pure and characterisable sample of the acetate derivative. A sample of acetal **303** was therefore treated with acetic anhydride in pyridine in the presence of DMAP. After chromatography, this yielded acetate **305** in 54% overall yield from juglone **301** with sufficient purity (Scheme 82).



Reagents and conditions: a) aq. $\text{Na}_2\text{S}_2\text{O}_4$, Et_2O ; b) conc. H_2SO_4 , Me_2CO , rt; c) Ac_2O , DMAP, pyridine, 54% over 3 steps.

Scheme 82: Conversion of Juglone **301** into Acetate **305**

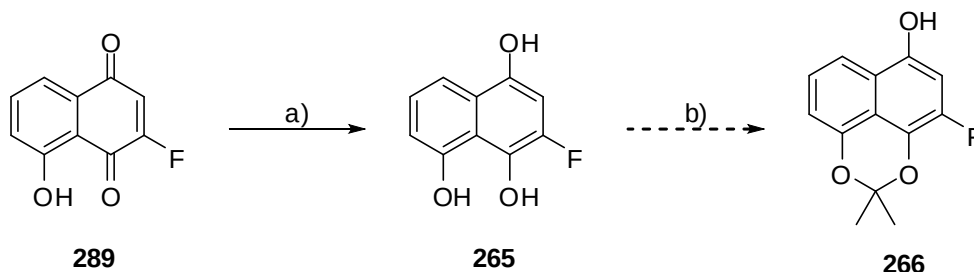
A sample of semi-purified acetal **303**, obtained as described previously, was also subjected to iodination conditions in order to determine whether this transformation was viable at this stage. **303** was treated with iodine in the presence of morpholine, but this yielded an unidentifiable mixture of decomposition products (Scheme 83). Variation of base or iodination agent gave no improvement and so attaching iodine at this point was not investigated further.



Reagents and conditions: a) base, e.g. morpholine, iodinating agent, e.g. I₂, CH₂Cl₂

Scheme 83: Attempted Iodination of Acetal **303**

With a synthesis of fluorojuglone **289** established, the established reduction and acetalisation described earlier was applied with **289** as the substrate (Scheme 84). However, the desired naphthol **266** was not isolated, and was only formed in a small amount as part of a chromatographically-inseparable mixture of products. The other conditions examined earlier were applied, but were also not successful for this transformation. It is known that the hydroquinone is formed without issue, but the acetalisation step fails to yield any of the desired product **266**.

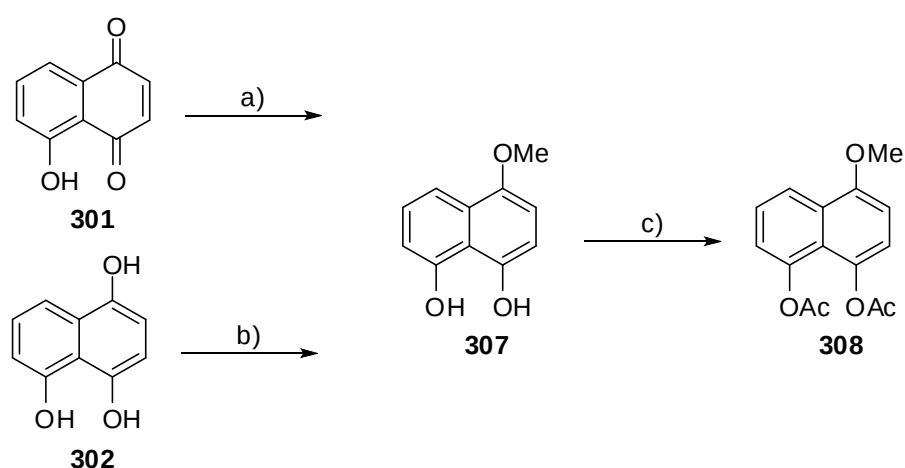


Reagents and Conditions: a) aq. Na₂S₂O₄, Et₂O; b) conc. H₂SO₄, Me₂CO or i) TMS-Cl, THF; ii) TMS-OTf, Me₂CO, CH₂Cl₂, -78 °C or TMS-OTf, Me₂CO, ROTMS (R = Me or *i*-Pr), CH₂Cl₂, -25 °C

Scheme 84: Attempted Synthesis of Naphthol **266**

Given the previous result this was disappointing as there was little difference between the substrates. The purity of the substrate was not an issue, but the differing electronic properties of the aromatic system imparted by the fluorine substituents clearly disfavoured the desired transformation proceeding. The products are unidentifiable as it seems that extensive decomposition took place. Therefore, alternative reactions which gave the same overall result were pursued for the model system.

Two different ways of synthesising monomethoxynaphthalene diacetates were described by Musgrave *et al.*,¹⁴² using methodology which could potentially be applied to this system (Scheme 85).



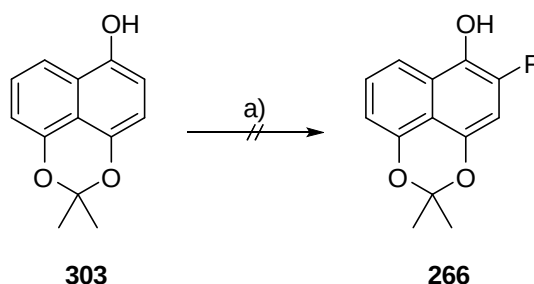
Reagents and Conditions: a) SnCl_2 , POCl_3 , MeOH ; b) i) NaBO_2 ii) Me_2SO_4 , NaOH ; c) Ac_2O , H^+ , 62% from **301**, 55% from **302**

Scheme 85: Musgrave's Syntheses of Diacetate **308**

However, when the 3-fluoro derivative **289** was used as the substrate, only low yields of intractable mixtures of products were obtained so these reactions were not investigated further.

As the acetalisation does work on the *des*-fluorojuglone, methods for using juglone and attaching fluorine after the acetalisation has taken place were then explored. The starting juglone **301** could be made from 2-fluoro-1,4-dimethoxybenzene using previous methodology, however as it is commercially available in this case it was purchased rather than synthesised.

The first procedure examined was electrophilic fluorination of naphthol **303**, which should occur exclusively *ortho* to the hydroxyl group when treated with an electrophilic source of fluorine. F-TEDA (Selectfluor™) was used in order to effect this transformation (Scheme 86).



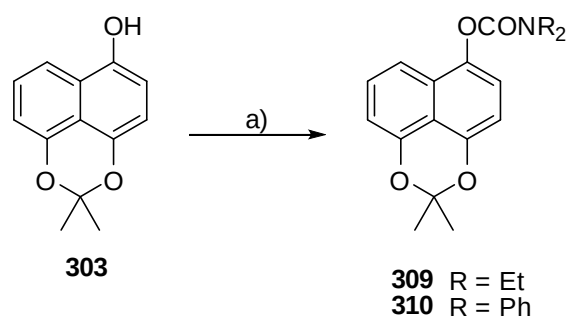
Reagents and Conditions: a) F-TEDA, MeCN

Scheme 86: Attempted Fluorination of Naphthol **303**

The reaction was unsuccessful however, producing only an intractable tar, the components of which could not be identified. This is probably due to the oxidative potential of F-TEDA, and the relative susceptibility to oxidation of the naphthol. Instead, a strategy entailing protection with an *o*-directing group, *o*-lithiation and quench with electrophilic fluorine was adopted.

The group chosen was the *O*-carbamate group, which has all the characteristics that are desired. It is also advantageous that the lithiated species can be quenched by other electrophiles to give rise to, for example, a hydroxyl group. Therefore, the conversion of **303** into the diethyl carbamoylated derivative **309** was investigated (Scheme 87).

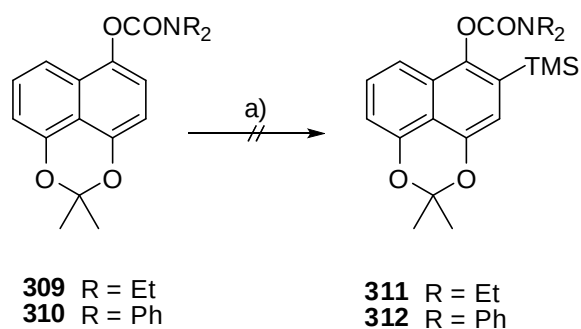
The diethyl carbamate was successfully synthesised using sodium hydride as a base; using a milder base, e.g. pyridine resulting in the reaction not going to completion, even with prolonged reaction times. It was also discovered that if naphthol **303** was used crude with no attempt to purify it beforehand, the yield over the three steps was higher than if it was purified prior to the carbamoylation. Over three steps, the carbamate can thus be obtained in a yield of 57%, with a high degree of purity. The diphenyl carbamate **310** was also synthesised by the same method in 49% yield over 3 steps.



Reagents and Conditions: a) NaH, ClCONEt₂, THF, 57% over 3 steps from **301** or NaH, ClCONPh₂, THF, 49% over 3 steps from **301**

Scheme 87: Carbamoylation of Naphthol **303**

The lithiation and electrophilic fluorination procedure was then investigated. Using *tert*-butyllithium in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) and quenching with trimethylchlorosilane gave the silylated product in varying degrees (Scheme 88). Even in identical conditions, the degree of lithiation was variable. In general, the reproducibility was poor, suggesting that the reaction is very sensitive to impurities or slight changes in reaction conditions and reagents (Table 4).



Reagents and Conditions: a) see Table 4, -78 °C

Scheme 88: Attempted Silylation and Fluorination of Aryl O-Carbamates **309** and **310**

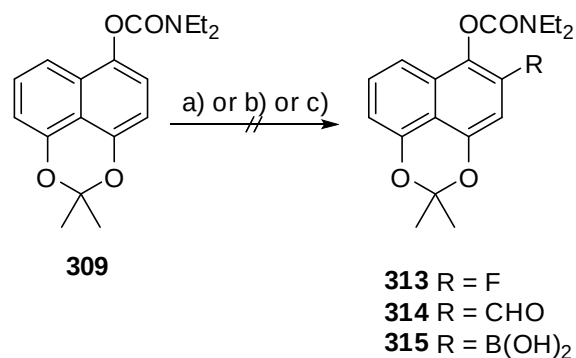
Entry	R	Base	Concentration (/M)	Solvent	Time (/h)	Ratio of starting material : product (: other)
1	Et	<i>s</i> -BuLi	1.0	THF	2	>95 : 5 >
2	Et	<i>t</i> -BuLi	0.5	THF	3	74 : 26
3	Ph	<i>t</i> -BuLi	0.5	THF	2	>95 : 5>
4	Et	<i>t</i> -BuLi	0.125	THF	2	59 : 41
5	Ph	<i>t</i> -BuLi	0.125	THF	2	65 : 19 : 15
6	Et	<i>t</i> -BuLi (2 eq)	0.5	THF	3	78 : 22
7	Et	<i>t</i> -BuLi	1.0	THF	3	44 : 56
8	Et	<i>t</i> -BuLi	0.5	Et ₂ O	3	30 : 21 : 49

Table 4: Trimethylsilylation of Aryl *O*-Carbamates **309** and **310**

It is clear that *sec*-butyllithium/TMEDA is ineffective at deprotonation at – 78 °C on the electron-rich system employed here (Entry 1). Use of *tert*-butyllithium/TMEDA is significantly better, but inconsistent results were still gained (Entry 2). Changing the nitrogen substituents on the carbamate from ethyl to phenyl did not seem to improve the yield (Entries 2-5). The diphenyl analogue gave inferior results to the diethyl, and importantly gave a side product, probably resulting from lithiation on the *N*-phenyl aromatic system (Entry 5). Noticeably, the diphenyl derivative, and/or its lithiated equivalent had superior solubility at the low temperatures (one of the reasons it was examined), but this did not translate into a better conversion, so the relative insolubility of the products was not a cause for the reluctance of the reaction. Concentration seemed to have an effect on the reaction, but it is unusual in that both increased and decreased concentrations seemed to give better conversions. However, due to the irreproducibility of this system generally, it is quite possible that these results are not indicative of the concentration, but of other factors.

The use of die thyl ether as a solvent was also investigated (Entry 8), and although the amount of starting material was comparatively lower, the major product was not the desired product, and LC-MS analysis indicated it contained no nitrogen, so presumably it is the result of decarbamylation.

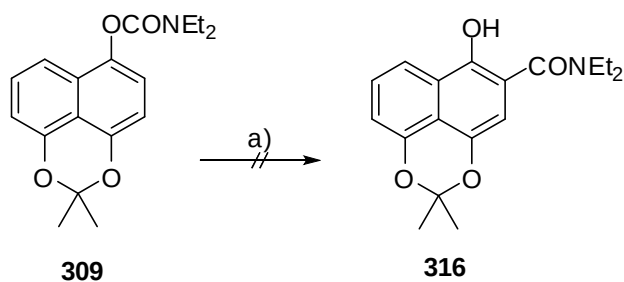
Similarly, the quenching of the lithiated species with F-TEDA or *N*-fluorodibenzenesulfonimide (NFSI) as electrophilic fluoride sources, or trimethyl borate or dimethylformamide as masked hydroxyl functionalities was unsuccessful and in each case returned starting material or complicated mixtures of products (Scheme 89).



Reagents and Conditions: a) i) *t*-BuLi, TMEDA, THF, $-78\text{ }^{\circ}\text{C}$, ii) NFSI, $-78\text{ }^{\circ}\text{C}$ or FTEDA $-78\text{ }^{\circ}\text{C}$;
 b) *t*-BuLi, TMEDA, THF, $-78\text{ }^{\circ}\text{C}$, ii) B(OMe)₃, $-78\text{ }^{\circ}\text{C}$; c) *t*-BuLi, TMEDA, THF, $-78\text{ }^{\circ}\text{C}$, ii) DMF, $-78\text{ }^{\circ}\text{C}$.

Scheme 89: The Attempted Borylation and Formylation of Carbamate **309**

It is clear that the fundamental reactivity of the aromatic core at $-78\text{ }^{\circ}\text{C}$ is an issue, as is not directly related to the choice of electrophile or substituents on the carbamate. Unfortunately the temperature cannot be warmed as the carbamate would undergo an anionic Fries rearrangement, described by Snieckus *et al.*¹⁴³ in which the $-\text{CONR}_2$ group is transferred to the aromatic ring from oxygen to carbon, producing *o*-hydroxyaryl amide **316**. Therefore, it was determined whether this proceeded cleanly on this substrate, and if so whether it could be utilised in the synthesis. However, on all occasions that the reaction was warmed above $-78\text{ }^{\circ}\text{C}$ complex mixtures of products were obtained (Scheme 90). Whether the carbamoyl group migrates or not, it is clear that the product of the reaction is not stable and is oxidising and/or polymerising and this route was not investigated further.



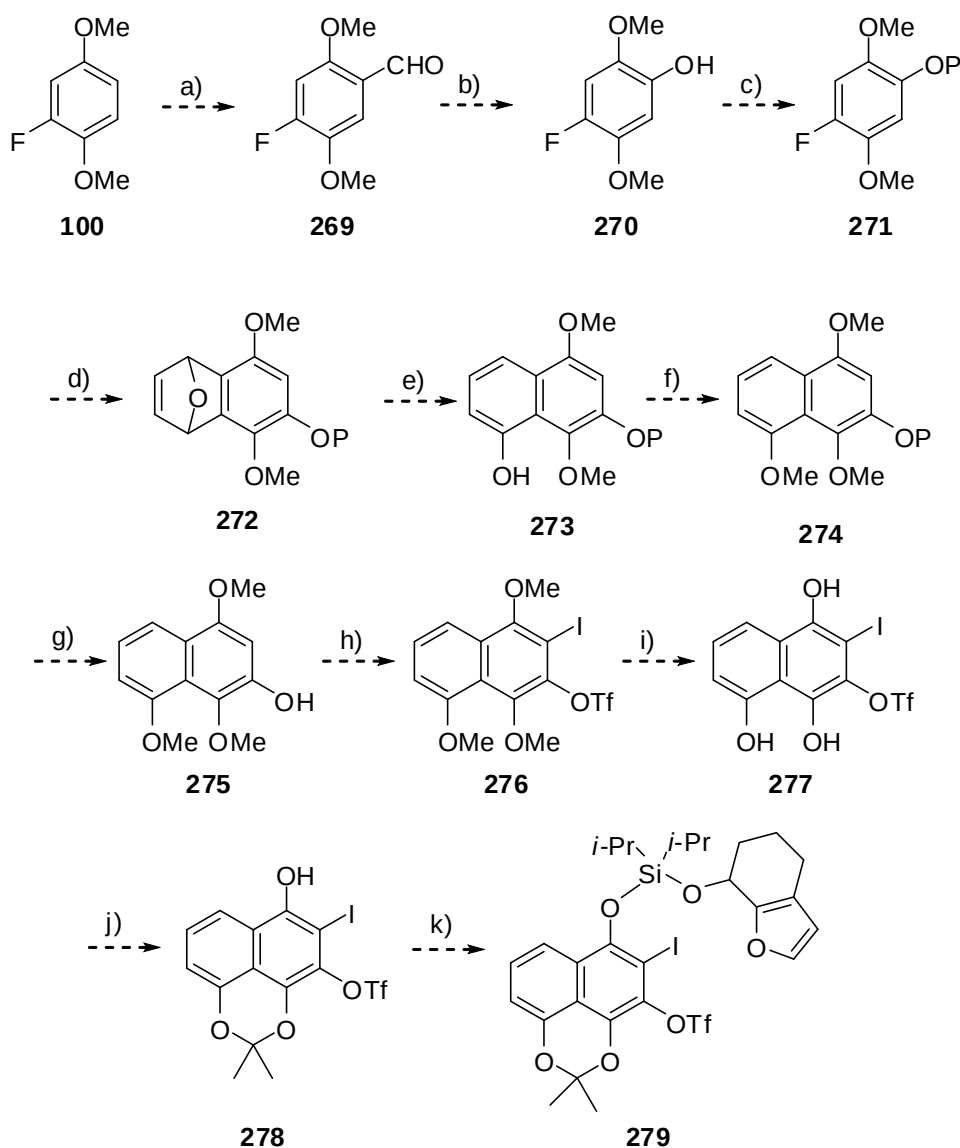
Reagents and Conditions: a) *t*-BuLi, TMEDA, THF, - 78 °C to rt

Scheme 90: Potential Anionic Fries Rearrangement of Aryl Carbamate **309**

At this juncture, the methodology of modifying the acetal **309** was discontinued. The use of other systems was then considered, but the simultaneous investigations into the iodotriflate aryne precursor are described.

5.5 Towards the Synthesis of Model Aryne Precursor 279

The proposed synthetic route to the iodotriflate naphthyne precursor **279** is detailed in Scheme 91. It is expected that this will provide a more accurate representation of the key intramolecular aryne-furan reaction and it is anticipated that some of this methodology can be used in the construction of the real system.

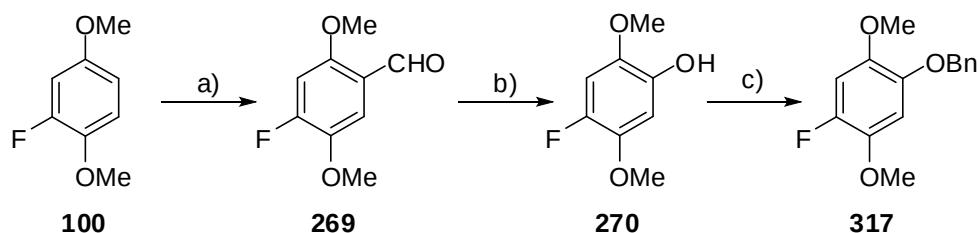


Reagents and conditions: a) i) SnCl_4 , Cl_2CHOMe , CH_2Cl_2 , ii) aq. HCl ; b) i) *m*-CPBA, CH_2Cl_2 ii) aq. NaOH ; c) protection; d) i) *n*-BuLi, THF, -78°C , ii) furan, -78°C to rt; e) aq. HCl , MeOH, Δ ; f) NaH, MeI, DMF; g) deprotection; h) i) base, I_2 ; ii) Tf_2O , base, CH_2Cl_2 ; i) BBr_3 , CH_2Cl_2 ; j) acetone, H^+ , k) NEt_3 , DMAP, **264**

Scheme 91: The Proposed Synthesis of Model Aryne-Furan Precursor **279**

The first step in the synthesis is the known regioselective formylation of 2,5-dimethoxyfluorobenzene **100**, using tin tetrachloride and methyl dichloromethyl ether.¹³⁶ The substitution occurs readily and after acidic work-up, aldehyde **269** was isolated in 84% yield. The subsequent step comprises a Dakin-like oxidation to afford phenol **270**. Treatment of **269** with *m*-CPBA in dichloromethane, followed by ethanolic aqueous sodium hydroxide to hydrolyse the corresponding formyl ester, gives the desired phenol **20** in 78% yield.

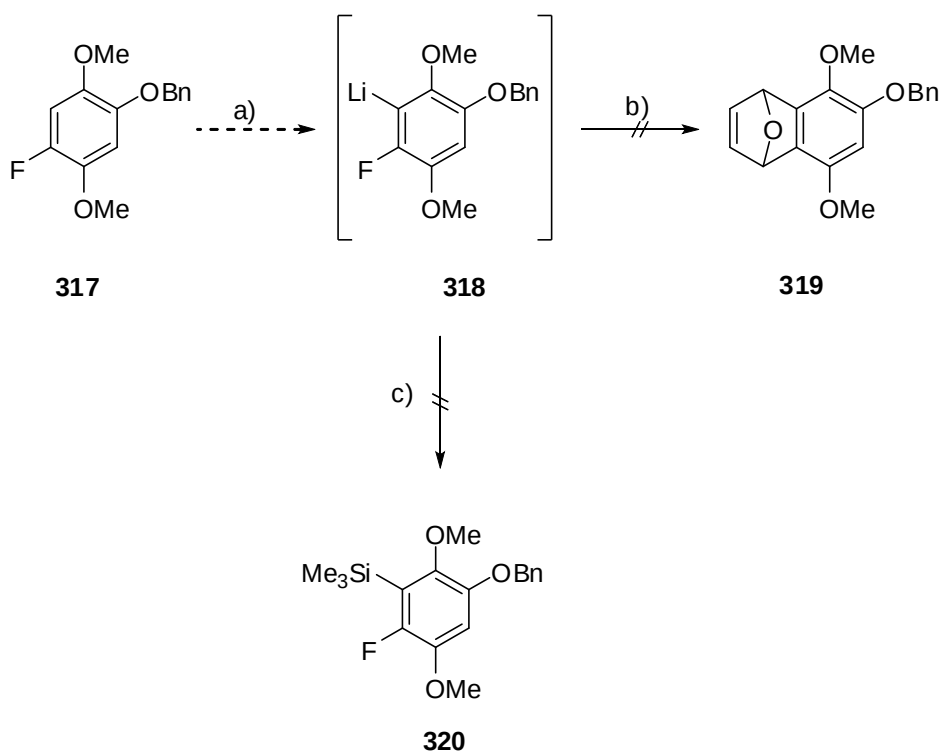
The hydroxyl group then required protection before generation of the aryne and for convenience the benzyl group was utilised, due to its ability to undergo selective deprotection with hydrogen and palladium on carbon. Standard benzylation conditions using benzyl bromide and potassium carbonate afforded benzyl ether **317** in a 93% yield. All three steps in this procedure were reproducible on larger scales (Scheme 92).



Reagents and conditions: a) i) SnCl_4 , MeOCHCl_2 , CH_2Cl_2 ; ii) HCl , H_2O , $0\text{ }^\circ\text{C}$, 84%; b) i) *m*-CPBA, CH_2Cl_2 , ii) NaOH , H_2O , EtOH , 78%; c) K_2CO_3 , BnBr , DMF , 93%

Scheme 92: Synthesis of Benzyl-Protected Aryne Precursor **317**

The first experiments were conducted using conditions that are known to generate arynes from aryl fluorides from previous work undertaken in the group,¹²⁹ i.e. lithiation with *n*-butyllithium at $-78\text{ }^\circ\text{C}$ with subsequent warming to room temperature to induce aryne formation in the presence of furan to trap the aryne as the cycloadduct (Scheme 93).



Reagents and conditions: a) *n*-BuLi, $-78\text{ }^{\circ}\text{C}$, THF or see Table 5, b) furan, $-78\text{ }^{\circ}\text{C}$ to rt; c) TMS-Cl, $-78\text{ }^{\circ}\text{C}$ to rt

Scheme 93: The Planned Synthesis of Cycloadduct **319** via Lithiated Species **318** and Attempted Trimethylsilyl Quench of **318**

However, this reaction resulted only in recovery of starting material (*ca.* 90%), with no other identifiable products. Therefore trimethylsilyl quenching experiments were undertaken (Scheme 93), to ascertain whether lithiation was occurring. A range of reaction conditions were employed to determine the reactivity of the starting compound to lithium bases (Table 5).

Entry	Base Used	Temperature (/ °C)	Conc. (/ M)	Time (/ min)	Yield of 320 (/ %)
1	<i>n</i> -BuLi	−78	0.30	20	-
2	<i>s</i> -BuLi	−78	0.30	20	-
3	<i>n</i> -BuLi	− 40	0.15	60	-
4	2.eq. <i>n</i> -BuLi	− 78	0.30	60	-
5	<i>t</i> -BuLi	− 78	0.30	30	-
6	<i>t</i> -BuLi	− 78	0.15	30	-
7	5 eq. <i>t</i> -BuLi	− 40	0.15	30	-

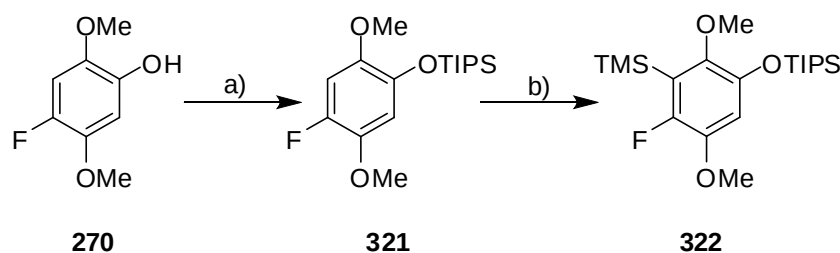
Table 5: Selection of Conditions Examined in Attempted Lithiation and Trimethylsilyl Quench of **318**

As is evident from Table 5 none of these reaction conditions were successful, and all resulted in starting material recovery in various yields along with various complex mixtures of other products. At 0.3 M the substrate was only partially soluble, but at lower concentrations where the substrate was soluble (Entries 3, 6, 7) the desired reaction still failed to proceed. The solubility of the substrate in different solvents, at − 78 °C and at − 40 °C was tested, but the substrate was found to be insoluble at these temperatures in diethyl ether, *tert*-butyl methyl ether, dimethoxyethane and 1M LiCl in THF.

The nature of the protecting group was reassessed in light of this lack of reactivity and it was decided to evaluate the reactivity of a silicon-based protecting group instead of benzyl, in order to determine whether the lack of reactivity was due to the benzyl group preventing or interfering with the reaction, or whether the additional oxygen was decreasing reactivity because it was making the aromatic system too electron-rich. The triisopropylsilyl group was chosen as the next group to be investigated, due to its known robustness, yet envisaged ease in removal.

The silyl ether was synthesised under standard conditions using tri-*iso*-propylsilyl triflate and triethylamine in dichloromethane to afford the desired silyl ether **321**

without incident in 89% yield. **321** was then subjected to the standard lithiation conditions and the chlorotrimethylsilane quench as before (Scheme 94).

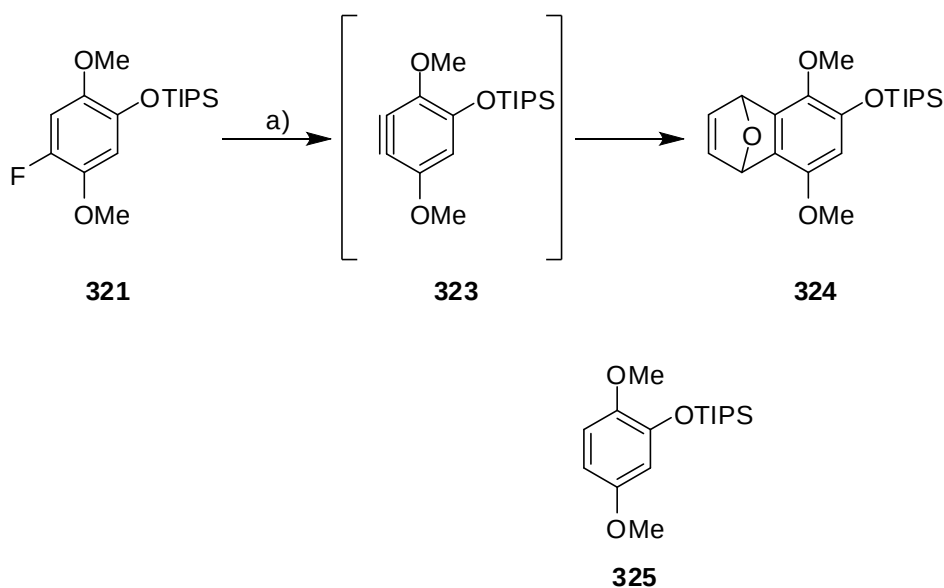


Reagents and conditions: a) NEt_3 , TIPS-OTf, CH_2Cl_2 , 89%; b) i) $t\text{-BuLi}$, $-78\text{ }^\circ\text{C}$, THF, 25 min, ii) Me_3SiCl , 95% (crude)

Scheme 94: Silyl Protection of **270** and Lithiation-Trimethylsilylation of **321**

When the initial conditions for the lithiation above were used ($n\text{-BuLi}$, $-78\text{ }^\circ\text{C}$, 25 minutes), it was found that there was 14% (by GC-MS) conversion to the silylated product. This result was certainly an improvement on the reaction of the benzyl ether equivalent, but still synthetically inadequate. The strength of the base was increased and when the transformation was attempted employing $t\text{-BuLi}$ in place of $n\text{-BuLi}$, it was found that the reaction went to 95% completion (by GC-MS) to the desired product. This indicates that the tri-*iso*-propylsilyl group altered the reactivity of the substrate enough that it is possible to form the lithiated species, though it was not determined whether the issue was caused by solubility, electronic or chemoselectivity factors.

The aryne formation and cycloaddition reaction sequence was then examined. When *tert*-butyllithium was used as base, with subsequent addition of five equivalents of furan and warming to room temperature the reaction proved to be successful, giving the desired cycloadduct **324** in a yield of 75%.

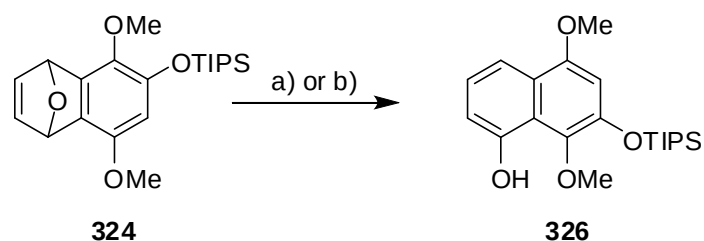


Reagents and conditions: a) i) *t*-BuLi, THF, – 78 °C, ii) furan, –78 °C to rt, 75%

Scheme 95: Cycloaddition Reaction of Furan and Aryne **323** Formed from Aryl Fluoride **321**

The reaction gave a minor side-product ($\leq 5\%$ by GC), which is believed to be defluorinated aryl silane **325** that, after chromatography, is isolated impure and thus not fully characterisable. However, the NMR and mass spectrometry data support this identification.

The procedure used previously in order to aromatise cycloadducts to naphthols comprised of hydrochloric acid in refluxing methanol. When this was employed in the aromatisation of cycloadduct **324**, despite evidence for some formation of the desired naphthol **326**, it was a minor component of the reaction mixture, as the conditions were sufficiently acidic enough to additionally desilylate the TIPS ether. Therefore, more mild conditions were examined. A procedure which has been used successfully on silyl ether-containing substrates¹²³ consists of using catalytic amounts of trifluoroacetic acid (TFA) in dichloromethane. When these conditions were employed (Scheme 96), they were successful, giving the desired naphthol **326** as a single regioisomer in a 90% yield.

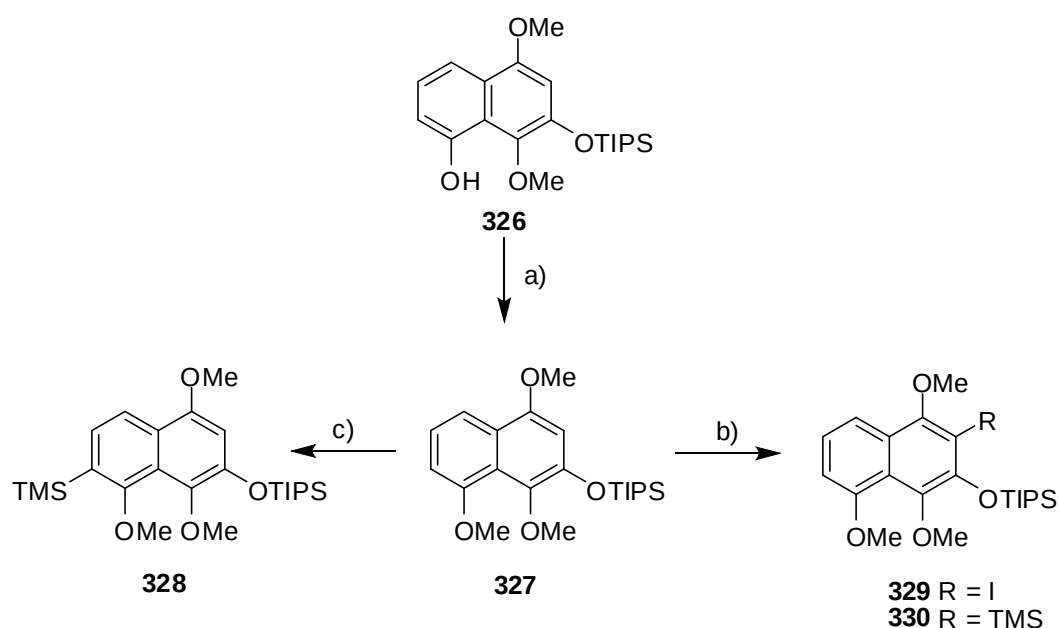


Reagents and conditions: a) 6 M HCl, MeOH, Δ ; 51%; b) CF₃CO₂H, CH₂Cl₂, 90%

Scheme 96: Acid-Catalysed Aromatisation of Cycloadduct **324**

The next step was the methyl protection of the naphthol, chosen as it can be deprotected with the other methyl ethers present on the molecule. The reaction proceeded in 86% yield under standard conditions (Scheme 97). Following this, the silyl-protected naphthol could be deprotected or the compound could be iodinated at this stage. As electrophilic iodination of a naphthol may present problems later on due to the electron-rich nature of the aromatic system, it was decided to attempt iodination at this stage in the synthesis.

Various reaction conditions were attempted for this transformation (Scheme 97, Table 6), but unfortunately none were successful in delivering the desired product, either returning starting material or decomposing to unidentifiable products. Again, a trichloromethylsilane quench was used to determine whether lithiation was the problem or the iodine electrophile. Significantly, when *sec*-BuLi was used as the base, and the mixture quenched with trichloromethylsilane, a silylated product was obtained along with some starting material. Unfortunately it was the 6-substituted product, **328**, not the desired 2-substituted, **330**. Despite this site being electronically favoured for lithiation, the TIPS group has been known to direct lithiation away from itself due to the steric constraints it imparts on the *ortho*-position.¹⁴⁴



Reagents and conditions: a) NaH, MeI, THF, 86%; b) see Table 6; c) i) *s*-BuLi, THF, −78 °C; ii) TMS-Cl

Scheme 97: Methylation of **326** and Attempts to Iodinate and Silylate **327**

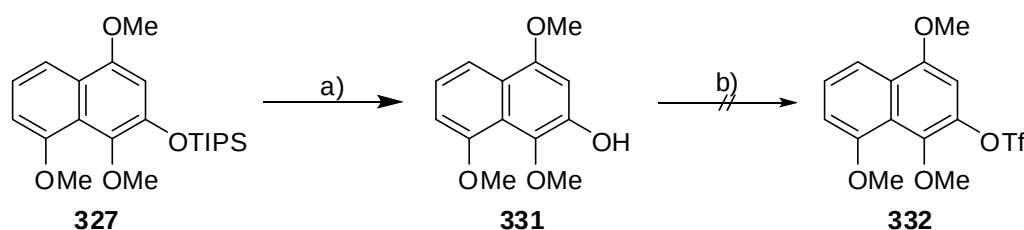
Entry	Iodinating Agent	Other Reagents	Solvent	Temperature (°C)	Result
1	I ₂	AgOTf	CHCl ₃	23	Decomp.
2	I ₂	AgO ₂ CCF ₃	CHCl ₃	23	Decomp.
3	I ₂	AgO ₂ CCF ₃ , NEt ₃	CHCl ₃	23	SM
4	NIS	CF ₃ CO ₂ H	MeCN	23	decomp.
5	ICl	-	CH ₂ Cl ₂	0	decomp.
6	I ₂	<i>n</i> -BuLi	THF	−78	SM
7	NIS	<i>n</i> -BuLi	THF	−78	SM

Table 6: Conditions Examined in Iodination of **327**

With this result, it was realised that iodination may prove difficult on this substrate, and that perhaps a less sterically demanding protecting group, e.g. the *tert*-butyldimethylsilyl (TBS) group, should be used in this synthesis.

Attention was then turned to the deprotection of the silyl ether and reprotection with the triflate group. This was initially performed with tetrabutylammonium fluoride (TBAF) and although the desired product is formed, according to ^1H NMR of the crude product of the reaction, this product appears to be largely unstable to chromatography on silica or alumina with less pure, low-yielding recovery. Recrystallisation was similarly unrewarding, with low yields of impure products. The product is also unstable in air, as decomposition was evident after two days.

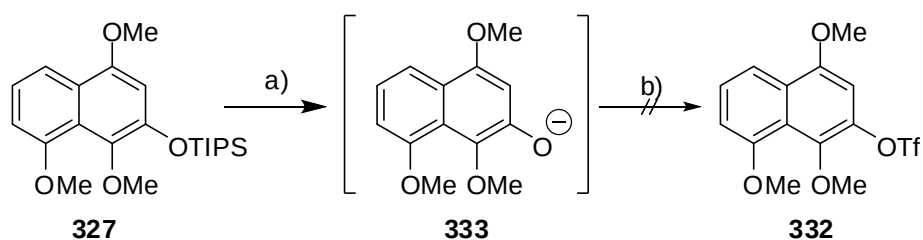
The next step in the sequence was triflation of the product, and this was attempted on the crude product using triflic anhydride and di-*iso*-propylethylamine. However this reaction was unsuccessful as the reaction only resulted in a complex mixture of decomposition products (Scheme 98).



Reagents and conditions: a) TBAF, THF; b) Tf_2O , *i*-Pr₂NEt, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$ to rt

Scheme 98: Fluoride Deprotection of Silyl Ether **327** and Attempted Triflation of **331**

Similarly, quenching the desilylation reaction with triflic anhydride, without isolating the naphthol was unsuccessful. The use of alternative fluoride sources, which circumvented the use of THF and water were also investigated, namely tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) and tetrabutylammonium triphenyldifluorosilicate (TBAT), both commercially available as pure, anhydrous solids. This meant that the one-pot procedure of desilylation and triflation could be carried out in dichloromethane (Scheme 99). In both cases, TLC analysis indicated consumption of the silyl ether, but the presence of the desired aryl triflate **332** was not detected. The use of *N*-phenylbis(trifluoromethanesulfonimide) as the triflating agent also failed.



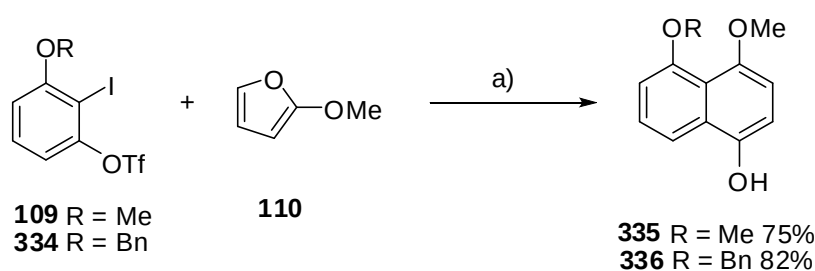
Reagents and conditions: a) TASF, CH₂Cl₂, 0 °C, 45 min or TBAT, CH₂Cl₂, 0 °C, 45 min; b) Tf₂O, –78 °C to 23 °C or PhNTf₂, –78 °C to 23 °C.

Scheme 99: The Attempted One-Pot Desilylation-Triflation of **327**

Even in the event of triflation, this would now preclude iodination with *ortho*-lithiation, and combined with the problems encountered with the corresponding fluoride model system involving the isopropylidene acetal, it was decided to focus away from this type of model system.

5.6 Towards the Synthesis of Model Aryne Precursor 260

A route to a similar type of structure is described by Suzuki,⁷⁶ made by an aryne-furan cycloaddition between furan **110** and the arynes derived from triflate **109** and **334**. With this precursor, the cycloaddition occurs at low temperatures and the extra oxygen functionality on the furan means that the cycloadduct undergoes spontaneous aromatisation to give naphthols **335** and **336** (Scheme 100).

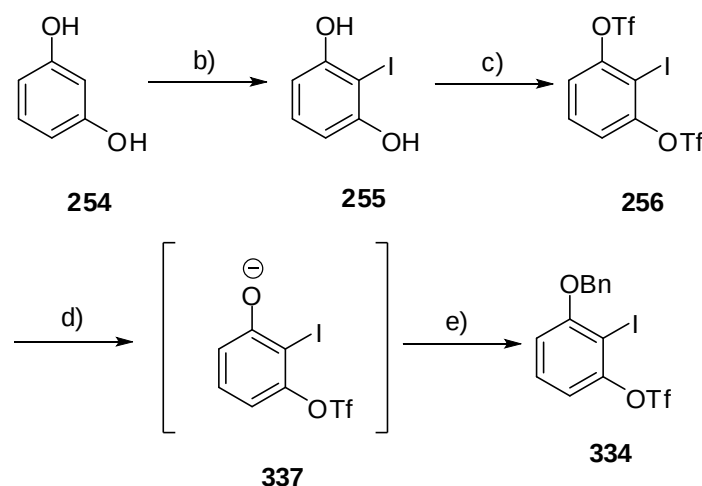


Reagents and conditions: a) *n*-BuLi, THF, –78 °C, 75-82%

Scheme 100: Suzuki's Synthesis of Naphthols **335** and **336** via Aryne-Furan Cycloaddition

The route to the starting triflates **109** and **334** is also documented by Suzuki *et al.*,¹³³ which is similar to the synthesis of iodotriflate precursor **257** described previously in Section 5.2. The benzyl ether **334** was successfully made in three steps from

commercially available resorcinol **254** as described by the literature. Selective iodination and triflation gave bis(triflate) **256** which was selectively hydrolysed with caesium carbonate and the resulting phenolate was quenched with benzyl bromide to give benzyl ether **334** in 53% overall yield from **254**.



Reagents and conditions: a) *n*-BuLi, THF, $-78\text{ }^{\circ}\text{C}$; b) I_2 , NaHCO_3 , H_2O , 71%; c) Tf_2O , *i*-PrNEt₂, CH_2Cl_2 , $-78\text{ }^{\circ}\text{C}$ to rt; d) Cs_2CO_3 , DME, $80\text{ }^{\circ}\text{C}$; e) BnBr, $25\text{ }^{\circ}\text{C}$, 74%, over 3 steps

Scheme 101: Synthesis of Aryne Precursor **334**

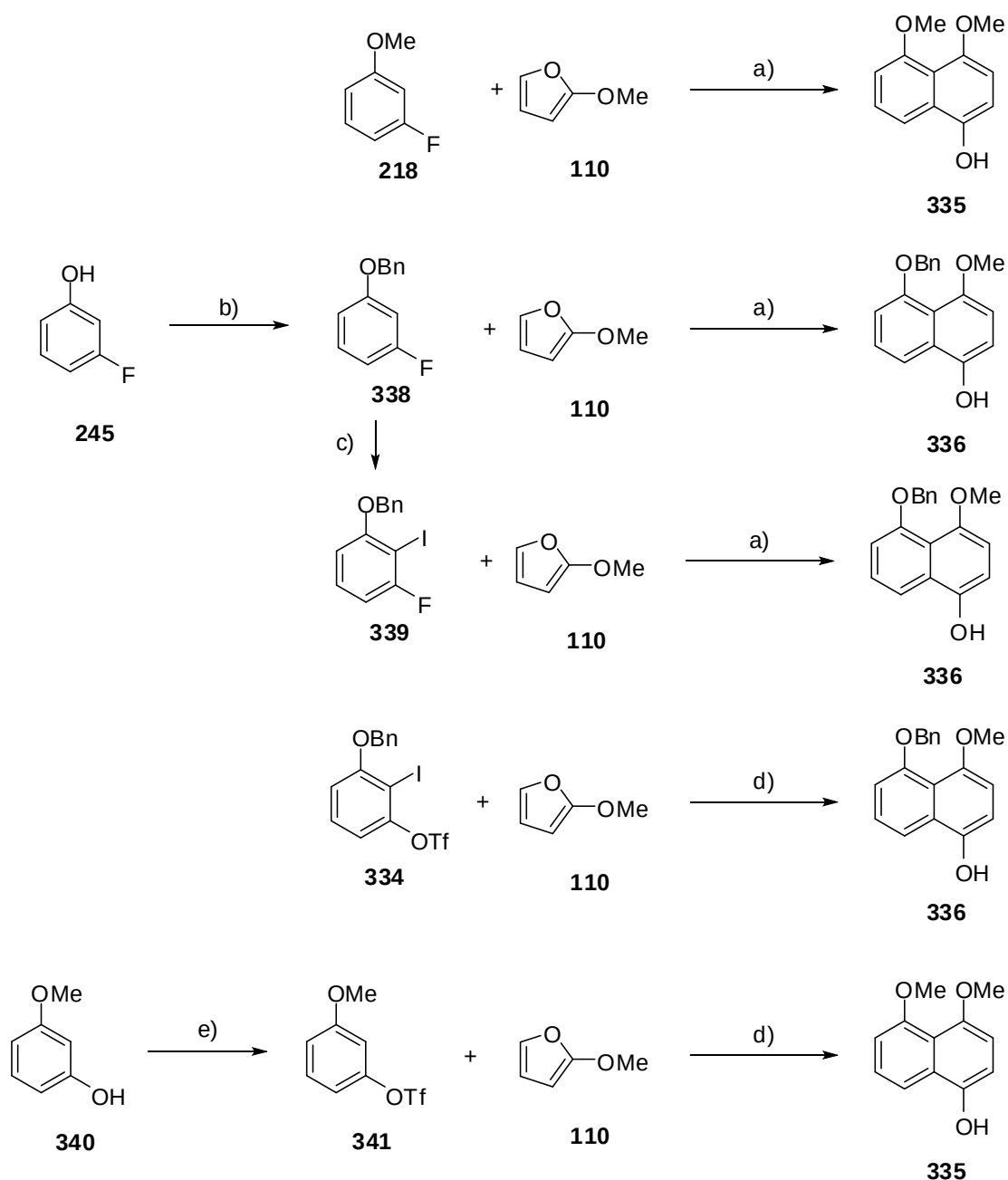
The *ortho*-iodophenyl triflate motif is an excellent aryne precursor in species such as **334**, enabling the halogen-lithium exchange, elimination to form the aryne, regioselective cycloaddition with 2-methoxyfuran, and aromatisation to deliver naphthols **335** in high yield and short reaction time. However, the synthesis of **334** is three steps from commercially available materials, and more easily-available aryne precursors were first tested. Even if the cycloaddition step is lower-yielding or longer times are required, they may impart a higher overall yield and lower reaction times to the naphthol core structure.

To this end, the aryne precursors **218**, **338**, **339** and **341** were targeted as they fulfilled the criterion of being readily available; **338** was available by benzylation of 3-fluorophenol, which proceeded in 89% yield, **218** is commercially available, and **341** was obtained by triflation of 3-methoxyphenol in 84% yield (Scheme 102).

With the aryne precursors in hand, attention was turned to the aryne generation-cycloaddition-aromatisation sequence. Aryl fluorides **218**, **338** and **339** were treated with *n*-butyllithium at $-78\text{ }^{\circ}\text{C}$ and then 2-methoxyfuran **110** was added and the

solution warmed to room temperature, whereas aryl triflate **341** was mixed with **110** at $-78\text{ }^{\circ}\text{C}$ and *n*-butyllithium was added to the mixture.

In all cases, the corresponding naphthol was synthesised in varying yields. The naphthols were somewhat unstable to chromatography, with some decomposition evident. In the case of the methyl-protected naphthol **335**, made from either **218** or **341**, the product was recrystallisable from chloroform, however the benzyl-protected naphthol **336**, from **338** or **339**, was not easily recrystallisable and so was used crude. The fluoride precursors gave the naphthol, but in lower yields than the triflate or iodotriflate precursors. As expected, the iodotriflate **334** was the best precursor in terms of yield for the cycloaddition step, but with the extended synthesis needed to obtain **334** the overall yields become comparable.

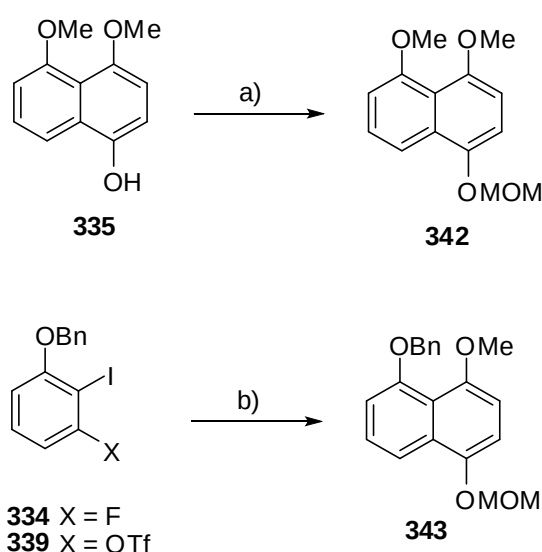


Reagents and conditions: a) i) *n*-BuLi, THF, $-78\text{ }^{\circ}\text{C}$, ii) **110**, $-78\text{ }^{\circ}\text{C}$ to rt, **335** 38%, **336** 42%; b) NaH, BnBr, DMF, 89%; c) i) *n*-BuLi, THF, $-78\text{ }^{\circ}\text{C}$, ii) I_2 , 74% d) *n*-BuLi, THF, $-78\text{ }^{\circ}\text{C}$, **336** 67%, **335**, 48%; e) Tf_2O , *i*-PrNEt₂, CH_2Cl_2 , $-78\text{ }^{\circ}\text{C}$ to rt, 84%.

Scheme 102: The Syntheses and Cycloaddition Reactions of **218**, **338**, **334** and **340**

With quantities of naphthol **335** and **336** in hand, protection could be examined. The carbamate had already proven to be unsatisfactory for further elaboration, but the MOM group, a good *ortho*-director, was an attractive alternative. It was not able to be used in the previous route because it would not be able to be selectively deprotected in the presence of the isopropylidene acetal, but in this system such a problem is not

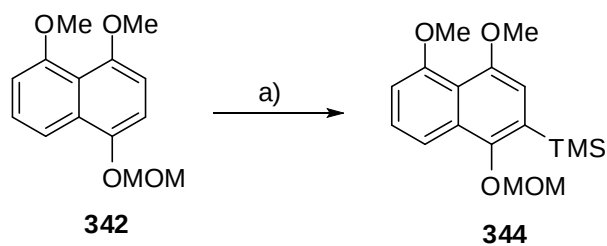
encountered. Formation of the MOM ether was then undertaken with sodium hydride and chloromethyl methyl ether to give ether **342** in high purity, with no starting material remaining, but with a surprisingly low yield of 55% after chromatography. Using caesium carbonate, potassium hexamethydisilazanide or triethylamine instead gave similar or lower yields. It was then discovered that direct addition of triethylamine and methyl chloromethyl ether to the cycloaddition reaction instead of quenching gave a better yield than that of the corresponding two-step reaction. This was also carried out with the benzyl ether **342**, and the overall two-step process yielded the ether **343** in 42% yield.



Reagents and conditions: a) NaH, MOMCl, DMF, 55% ; b) i) *n*-BuLi, **110**, THF, -78 °C, ii) NEt₃, MOMCl, **342** 40%, **343** 42%

Scheme 103: The Formation of Ethers **342** and **343**

With a quantity of ether **342** in hand, the lithiation could also be tested and for convenience, chlorotrimethylsilane was used an electrophile to trap the aryllithium intermediate, forming **344** (Scheme 104). A variety of conditions were tested and the results are displayed in Table 7.



Reagents and conditions: a) see Table 7

Scheme 104: Attempted Lithiation and Chlorotrimethylsilane Quench of **342**

Entry	Base	Temperature (°C)	Result
1	<i>n</i> -BuLi, TMEDA	0	Complex mixture
2	<i>n</i> -BuLi	0	Complex mixture
3	<i>n</i> -BuLi	−78	8% conversion
4	<i>s</i> -BuLi	−78	5 % conversion
5	<i>t</i> -BuLi	−78	6% conversion
6	<i>n</i> -BuLi	−30	30% conversion
7	<i>n</i> -BuLi	−10	37% conversion

Table 7: Attempted Trimethylsilylation of Ether **342**

None of the results are satisfactory in terms of conversion or purity; when the reaction is sufficiently warm to react it appears to react at multiple sites. At this juncture, the whole concept involving functionalising the aryne precursor in this way was discontinued as it was felt that there was a common lack of reactivity when functionalising aromatic systems in this way and that the yields were consistently average and often irreproducible.

5.7 Towards the Synthesis of Bromide Aryne Precursors **345** and **346**

An alternative route to bromide aryne precursor systems was then considered; dibromide system **345** and an *ortho*-bromoophenyl triflate system **346**.

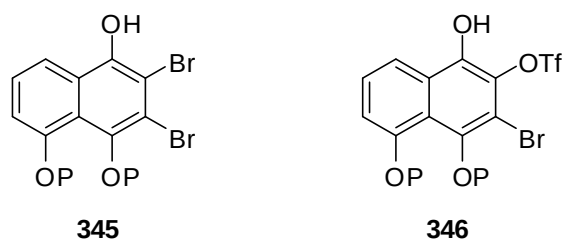
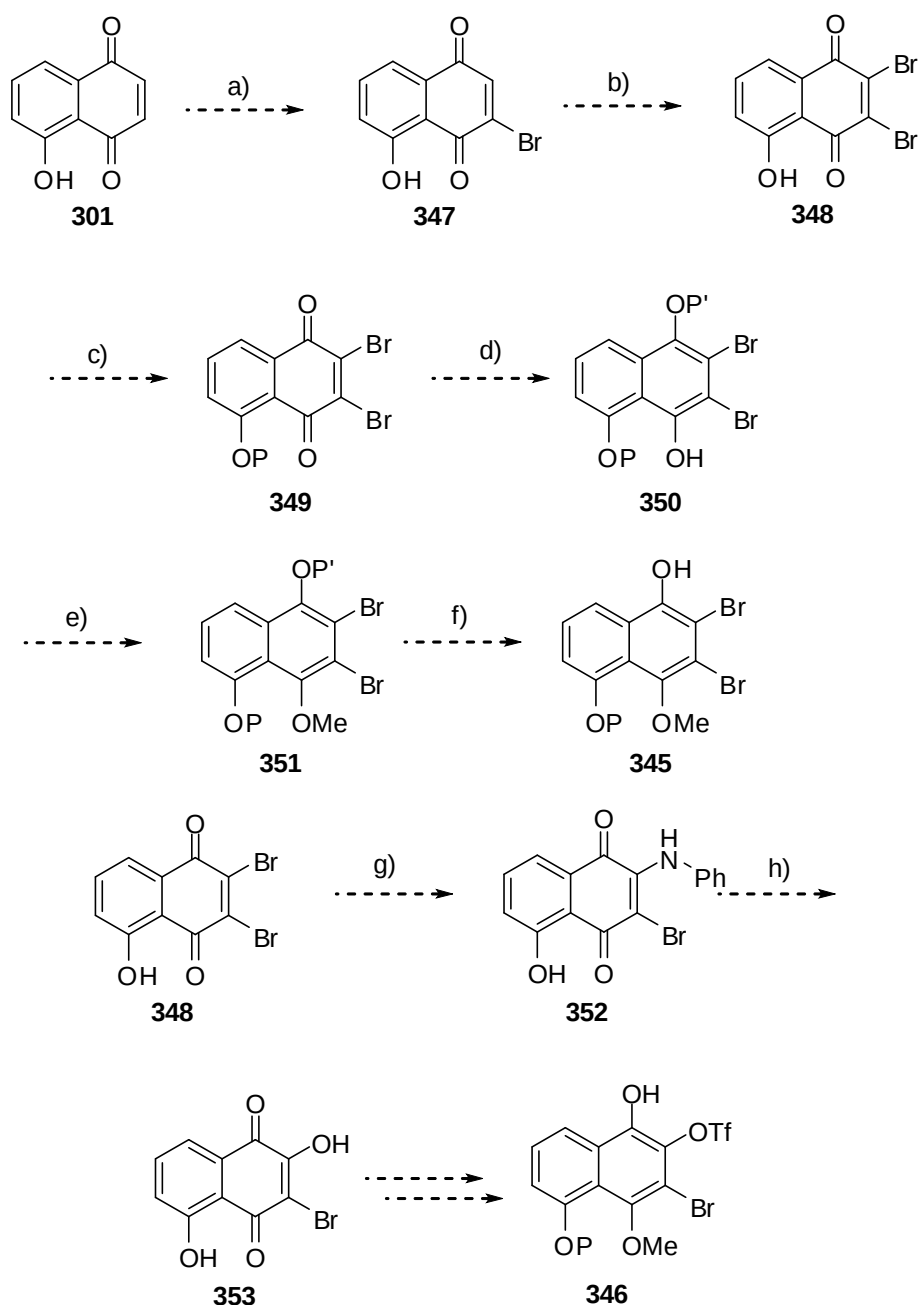


Figure 8: Bromine-Based Aryne Precursors **345** and **346**

A proposed synthetic route to aryne precursors **345** and **346** is described in Scheme 105. 5-Hydroxy-1,4-naphthoquinone (juglone, **301**) can be converted in two steps to the known dibromojuglone **348**^{145,146} using bromine in acetic acid as the bromine source in both cases. This is carried out in a stepwise manner because in the first bromination, the reaction proceeds more cleanly if the dibromide intermediate is isolated before thermal elimination of HBr is undertaken.

The hydroxyl group of dibromojuglone **348** can then be protected, and then the use of zinc in acetic anhydride¹⁴⁷ to reduce the quinone functionality and selectively acetylate the less hindered hydroxyl group of the hydroquinone will be examined. Alternatively, reduction with aqueous sodium dithionite and subsequent selective protection of the hydroquinone in the 1-position¹⁴⁸ will be examined, as the 4-position is disfavoured due to the *peri* effect.¹⁴⁹ The remaining hydroxyl group can be methylated, and the 1-position deprotected to reveal the desired naphthol **345**.

Additionally, the dibromojuglone intermediate **348** can be transformed into the known anilinobromojuglone **352**¹⁴⁶ by reaction with aniline. This compound can then be further elaborated to the known 2-hydroxyl derivative by heating in an acidic solution.¹⁵⁰ This then sets all the functionalities in place for the desired *ortho*-bromoaryl triflate **355** which should be attainable by reduction and functional group manipulation.

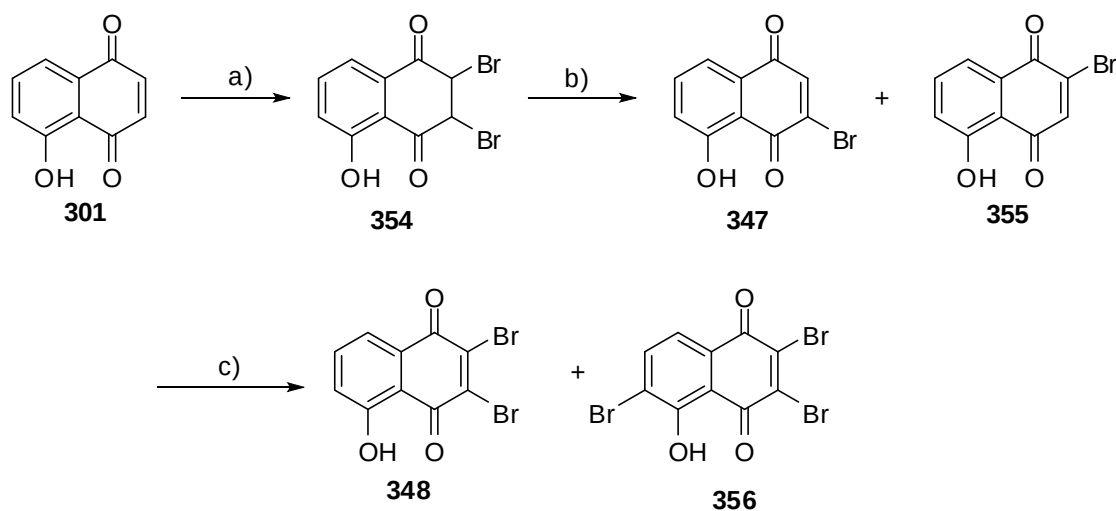


Reagents and conditions: a) Br_2 , AcOH , ; b) Br_2 , AcOH , Δ ; c) protection; d) i) $\text{Na}_2\text{S}_2\text{O}_4$, ii) selective protection; e) base, MeI ; f) deprotection; g) PhNH_2 , Δ ; h) H_2SO_4 , Δ

Scheme 105: Proposed Synthetic Route to Aryne Precursors **345** and **346**

Thus, juglone **301** was converted into 3-bromojuglone **347** via the dihydrodibromojuglone intermediate **354**. Thermally-induced elimination of HBr to reform the quinone system strongly favours the 3-bromojuglone isomer over 2-bromojuglone, and any 2-bromojuglone that does form is removed during recrystallisation, though it is inconsequential to the synthesis, as the next step is

bromination in the 2-position. In the event, **347** was formed successfully in 82% yield and was subsequently heated with bromine in acetic acid, with dibromojuglone **348** the expected product. This transformation however only yielded mainly the tribromojuglone compound **356** (Scheme 106).



Reagents and conditions: a) Br₂, AcOH; b) EtOH, Δ, 82% over 2 steps, **347**:**355** 95:5; c) see Table 8

Scheme 106: The Conversion of Juglone **301** to Bromojuglone Derivatives **347** and **356**

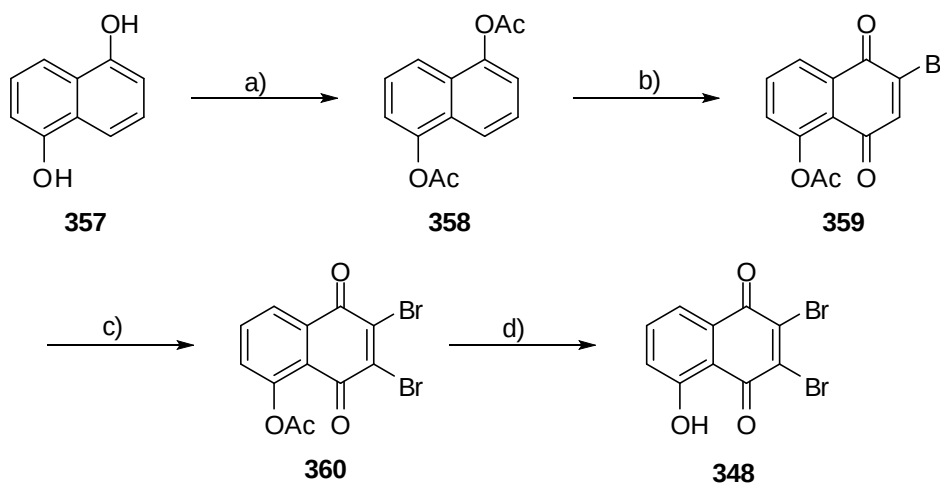
As this procedure did not yield the desired compound, modifications were made in order to try and selectively brominate at the double bond. The results are shown in Table 8.

Entry	Temperature (/ °C)	Equiv. of Br ₂	Yield (%)	% of 347 (SM) in product	% of 348 in product	% of 356 in product
1	90	1.5	68	0	0	100
2	23	2.0	62	?	?	?
3	80	1.0	48	0	5	95
4	55	2.0	70	0	75	25
5	55	1.2	86	15	55	30
6	55	1.0	78	11	82	7

Table 8: The Bromination of **347**

It was evident that at high temperatures, bromination would readily occur twice on the same molecule, and that the only product that precipitated out was the tribrominated compound **356** (Entries 1 and 3). At room temperature, however, a complex mixture of compounds was formed (Entry 2). NMR analysis indicated a complex mixture of unidentifiable products. In contrast, at 55 °C more successful results were obtained. At this temperature, the main product was the desired dibrominated compound, **348**. With excess bromine, tribromide **356** is also formed in varying quantities (Entries 4 and 5), but only one equivalent of bromine is used, both **356** and starting monobromide **347** are only present in small amounts (Entry 6). On recrystallisation, the desired compound is obtained pure, but at expense of yield. All three juglones are chromatographically inseparable, meaning this method of purification is not viable for this reaction sequence.

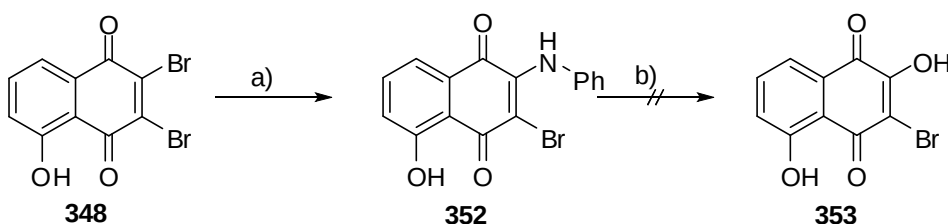
In an effort to increase the yield of dibromojuglone **348**, another synthetic route was examined. This involves the regioselective formation of the known 2-bromojuglone acetate, **359**, from naphthalene-1,5-diol diacetate, **358**.¹⁵¹ The diacetate was formed from the diol without incident in 92% yield and the oxidative bromination was also successful in 76% yield to give the acetate **359**. It was envisaged that upon treatment with bromine the acetate will discourage unwanted *ortho*-bromination in the 6-position, and will only brominate the double bond in the 3-position. At 55 °C, this reaction occurs readily to give **360**, though if excess bromine or higher temperatures are used then bromination does still occur to some extent in the 6-position. At 80 °C the acetate began to undergo hydrolysis, though the opportunity to use this as a synthetically useful transformation is limited as bromination is then more favoured in the *ortho*-position and a mixture of various brominated products of the hydrolysed and unhydrolysed product is obtained. The hydrolysis of the acetate group was achieved in a separate step, using a Brønsted acid, to give the desired dibromojuglone **348** in reasonable yield (Scheme 107).



Reagents and conditions: a) Ac_2O , $\text{C}_6\text{H}_5\text{N}$, 92%; b) NBS, $\text{AcOH}/\text{H}_2\text{O}$, 65 °C, 76%; c) Br_2 , AcOH , 55 °C, 85% ; d) aq. H_2SO_4 , EtOH , Δ , 70%

Scheme 107: The Conversion of Diol **357** into Dibromojuglone **348**

Thus two routes to the dibromojuglone intermediate **348** were established. The conversion to the hydroxybromojuglone was examined, which involved the conversion of the dibromojuglone **348** into the anilobromojuglone compound **352** by heating in the presence of aniline (Scheme 108). This was successfully achieved in a high yield (83%). However, the second step is less rewarding. It is described in the literature¹⁵⁰ that heating with aqueous acid will deliver the hydroxybromide **353** but under the conditions described the desired product was obtained with an unsatisfactory yield and purity. The time, temperature and acid were all varied, but emulating the literature result for this transformation proved elusive.

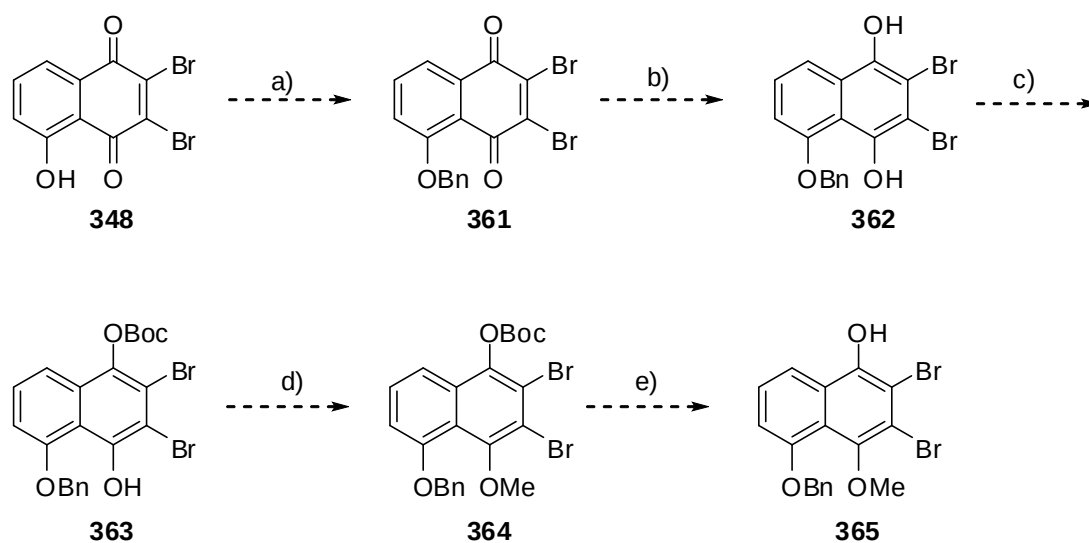


Reagents and conditions: a) PhNH_2 , EtOH , Δ , 83%; b) aq. H_2SO_4 , Δ

Scheme 108: The Attempted Conversion of Dibromojuglone **348** into Hydroxybromojuglone **353**

With juglone **348** in hand, the following strategy was formulated. The hydroxyl group of **348** is protected as the benzyl ether, as it can be selectively removed at a later

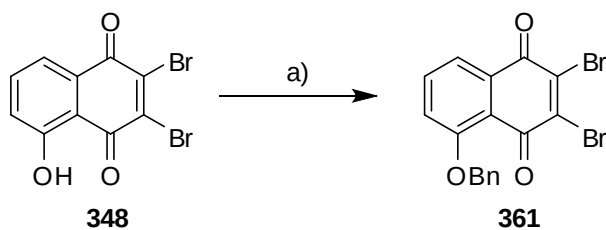
stage. The quinone can then be reduced, and it is anticipated that the two hydroxyl groups of the hydroquinone are sufficiently differentiable due to steric congestion from the benzyl group at the *peri*-hydroxyl group so that the 1-position can be selectively protected with a suitable electrophile; the initially chosen group was the *tert*-butyl carbonate (Boc) group for its ease in formation and ability to be selectively removed. The other hydroxyl group can then be protected as the methyl ether, and then the Boc group removed to give the naphthol **365** (Scheme 109).



Reagents and conditions: a) benzylation; b) reduction, c) Boc protection; d) methylation; e) Boc deprotection

Scheme 109: The Planned Synthetic Route to Naphthol **365**

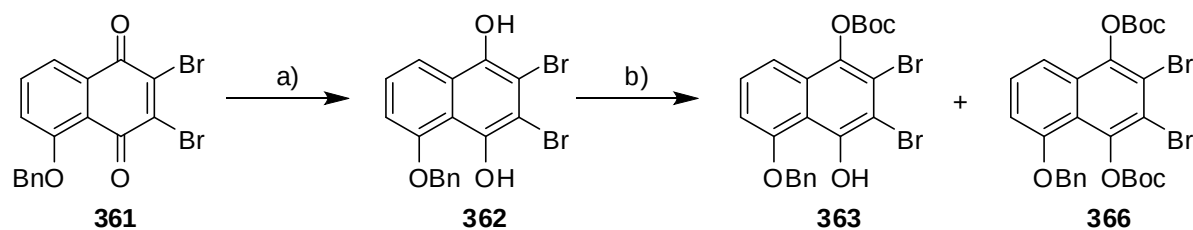
The standard conditions for benzyl ether formation (i.e. K_2CO_3/NaH and benzyl bromide in THF or DMF) are not usually used on juglone systems, presumably because of the instability of the juglone anion. Instead, the reaction is kept as near neutral as possible, and a method that has been previously shown to be successful is the use of silver(I) oxide and benzyl bromide in a chlorinated solvent.¹⁵² This procedure was applied successfully here to give benzyl ether **361** in 81% yield (Scheme 110).



Reagents and conditions: a) Ag_2O , BnBr , CHCl_3 , 81%

Scheme 110: Benzylation of Juglone **348**

The reduction of benzyl ether **361** was then examined. Sodium dithionite was used as the reducing agent and the corresponding hydroquinone **362** was formed. As is typical for naphthohydroquinones, it is unstable to purification or long-term storage unless stored rigorously under an inert atmosphere as aerial oxidation back to the quinone is facile. Therefore hydroquinone **362** was usually used immediately after isolation. The conversion to carbonate **363** was then investigated (Scheme 111).



Reagents and conditions: a) aq. $\text{Na}_2\text{S}_2\text{O}_4$, CH_2Cl_2 ; b) see Table 9

Scheme 111: Reduction of Quinone **361** and Subsequent Boc-Protection of Hydroquinone **362**

Entry	Acylating Reagent	Concentration (/M)	Temperature (/ °C)	Time (/ hours)	Yield (/%)
1	A	0.2	25	1.5	0-21
2	A	0.1	0	1	0-12
3	A	0.05	– 15	1	25-54
4	A	0.05	– 40	1	0 ^a
5	A	0.1	– 78 to 23	15	24
6	B	0.3	23	48	0 ^a
7	B	0.3	80	1	0 ^b

a: only starting material recovered, b: uncharacterisable mixture of products obtained

Carbonation Reagent A: 1.0 eq. Boc₂O, 0.05 eq. DMAP, CH₂Cl₂

Carbonation Reagent B: 1.0 eq. BBDI, PhH

Table 9: Selection of Conditions Examined for the *tert*-Butylcarbonation of **362**

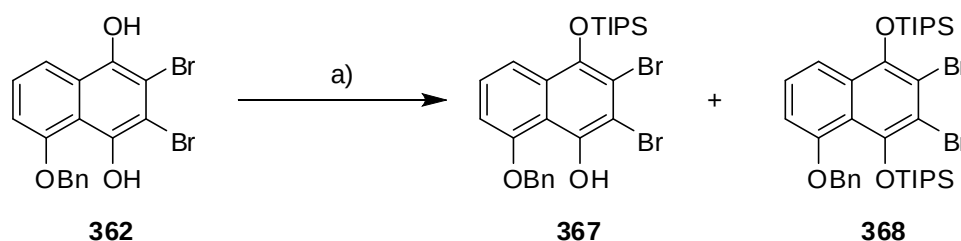
The use of di-*tert*-butyl carbonate as a carbonation agent is ubiquitous and was therefore examined first. It was hoped that the *peri*-effect would mean that there was clear differentiation between the two hydroxyl groups in the hydroquinone. However, treatment of a solution of hydroquinone with di-*tert*-butyl carbonate at room temperature (Entry 1) gave a mixture of products formed; three separate species were evident by TLC analysis. After chromatography, they were revealed to be the desired product **363**, the di-*tert*-butylcarbonated product **366**, and the re-oxidised starting material, quinone **361**. Almost complete chromatographic separation of quinone **361** from **363** and **366** was possible, but **363** and **366** significantly co-eluted, with only small amounts of each species able to be isolated pure. This also meant that it was difficult to accurately determine the proportion of the products.

At lower temperatures, and at decreased concentrations to ensure complete solubility at these temperatures, a higher proportion of the desired product **363** was obtained and at – 15 °C (Entry 3) the proportion appeared most favourable, with almost negligible amounts of **366** and the separable original quinone **361** as the only other product. However, it was discovered that the reaction is sensitive to small changes and the reproducibility is not perfect.

At temperatures lower than $-15\text{ }^{\circ}\text{C}$, the hydroquinone precipitated out of solution, even at high dilution, which ensures that no reaction occurs if the temperature is maintained at that level (Entry 4). If these experiments are subsequently allowed to warm up (Entry 5), the reaction will occur, though there is greater irreproducibility in such a procedure so was not deemed suitable.

The alternative acylating agent 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-1,2-dihydro-isoquinoline (BBDI) was also investigated but was not reactive enough under the conditions employed (Entry 6) and upon heating gave an intractable mixture of products (Entry 7) so was not investigated further.

As the carbonate group is relatively easy to form, it will not be as selective as other protecting groups and therefore other bulky protecting groups that are slower to form were considered. The triisopropylsilyl (TIPS) group was considered and thus hydroquinone **362** was subjected to standard silylation conditions (Scheme 112).

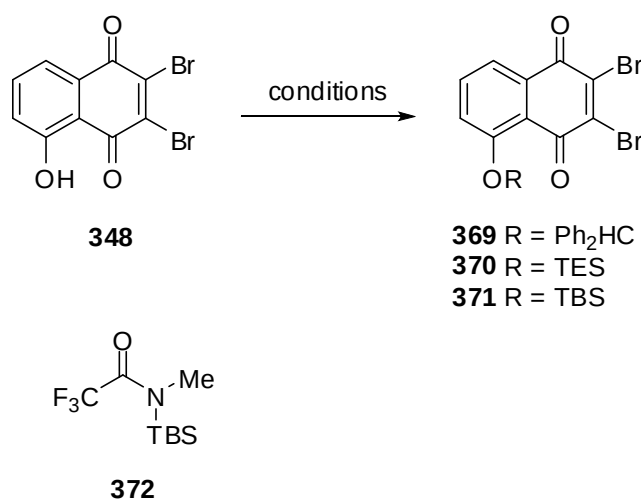


Reagents and conditions: a) imidazole, TIPS-Cl, CH_2Cl_2 , 46%, **367**:**368**, 1:1

Scheme 112: Silylation of Hydroquinone **362**

Surprisingly, in all cases a mixture of products was observed, where the bis-TIPS protected compound **368** was formed in an approximately 1:1 ratio with the desired mono-TIPS protected compound **367** in modest yield. The compounds were chromatographically inseparable. Approximately 20% of quinone **361** was also isolated. Due to the modest yield and unpromising selectivity issue this group was not explored further.

With a lack of success in the selective functionalisation of the hydroquinone with a *peri*-benzyl-protected ether, attention was turned to other forms of protecting group in the 5-position to offer more steric congestion. Accordingly, the diphenylmethyl ether, TBS and triethylsilyl (TES) protecting groups were examined (Scheme 113, Table 10).



Scheme 113: The Functionalisation of Juglone **348**

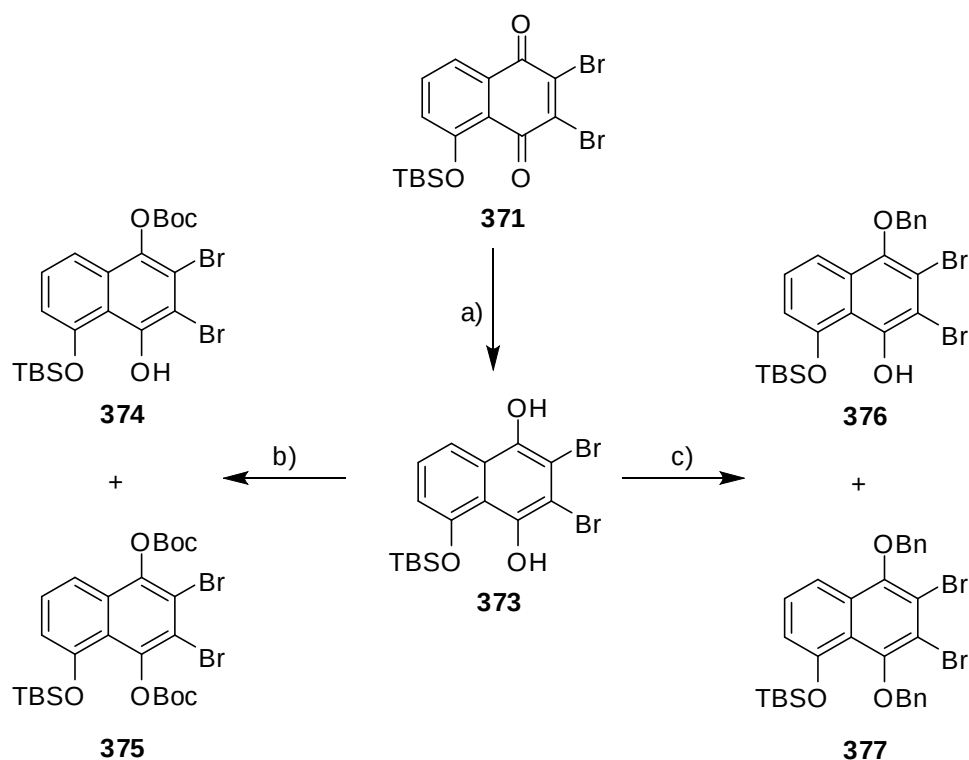
Entry	R	Conditions	Temperature (/°C)	Time (/h)	Product and Yield (/%)
1	Ph ₂ HC-	Ph ₂ CHBr, Ag ₂ O, CHCl ₃	60	48	369 , -
2	TES	Ag ₂ O, TESCl, CHCl ₃	60	24	370 , < 2
3	TBS	Ag ₂ O, TBSCl, CHCl ₃	60	24	371 , < 2
4	TBS	10 eq. MTBSTFA, 1% TBSCl, MeCN	82	0.5	371 , 84
5	TBS	4 eq. MTBSTFA, 1% TBSCl, MeCN	82	3	371 , 82

Table 10: Functionalisation of Juglone **348**

The attachment of the diphenylmethyl group, the triethylsilyl and *tert*-butyldimethylsilyl ethers were attempted under similar conditions as the benzyl ether,

using silver (I) oxide. The formation of the diphenylmethyl-protected compound **369** was unsuccessful (Entry 1), even with extended reaction times and heating. Silylation of **348** using silver (I) oxide conditions on both the TES and TBS ethers was also unsuccessful (Entries 2 and 3). However, the use of an alternative silylating agent, *N*-methyl-*N*-*tert*-butylsilyldimethyltrifluoroacetamide (MTBSTFA, **372**)¹⁵³ for the synthesis of TBS ethers delivered the silyl-protected ether in good yield. The reagent is commercially available at a high cost and it was found more practical to synthesise it from *N*-methyltrifluoroacetamide and *tert*-butyldimethylchlorosilane. The original literature procedure for the silylation of juglones¹⁵⁴ uses 10 equivalents and the reaction goes to completion after 30 minutes (Entry 4), but it was found silylation will proceed with no detriment to the yield with fewer equivalents of reagent and only a moderate increase in reaction time, viz. 4 equivalents for 3 hours (Entry 5).

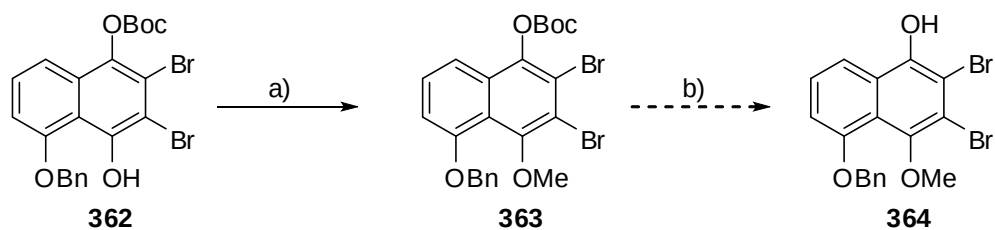
The selective functionalisation of **373** was then investigated. Reduction of **371** was successful as before to give hydroquinone **373**, and then the two protecting groups examined were the Boc group and the benzyl group (Scheme 114). The hydroquinone was subjected to acylation conditions as described previously, but the improved solubility of the hydroquinone meant that the reaction could be performed at $-78\text{ }^{\circ}\text{C}$. This seemed to decrease the relative amount of the doubly-acylated product **375**, but the overall yield and purity of the desired product **374** was not enhanced because of this. The product was recovered, after chromatographic purification, somewhat impure and even with generous estimates for the amount of impurity, the yield is approximately only 40%. The benzylation reaction proceeded and the singly-benzylated species **376** was the main product, but the doubly-benzylated species **377** was inseparable from the desired product and further small amounts of impurities were also present. Moreover, the yield of the desired benzyl ether **376**, even if pure, was modest as the total product recovery was only about 50%. Therefore, as in both cases the isolation of the desired species was with unsatisfactory yield and level of purity, the use of this species as an aryne precursor was discontinued.



Reagents and conditions: a) aq. $\text{Na}_2\text{S}_2\text{O}_4$, CH_2Cl_2 , 95% (crude); b) 1.0 eq. Boc_2O , 5 mol% DMAP, CH_2Cl_2 , -78°C , 40% 4:1, **374:375**; c) K_2CO_3 , BnBr , THF, 50%

Scheme 114: The Functionalisation of Hydroquinone **373**

Returning to the most reliably synthesised species, a small amount of the singly-protected hydroquinone **362** was carried forward in a test reaction. The naphthol was methylated to provide ether **363**, and although the reaction was unoptimised due to the scale of the reaction, it was sufficient to test out deacylation step. Unfortunately, all conditions employed (Scheme 115), both acidic and basic, gave an intractable mixture of products, amongst which the desired naphthol **364** was not identified. In all cases the reaction mixture assumed a dark-orange colour, suggesting probable quinone or quinone-type products resulting from oxidation and polymersiation.



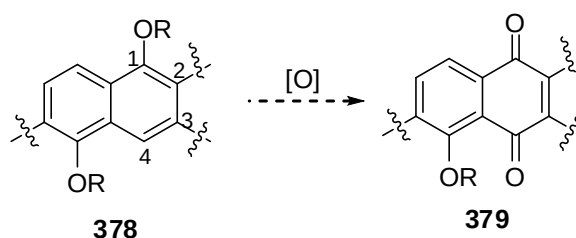
Reagents and conditions: a) NaH, MeI, THF, 74% ; b) various acidic and basic conditions, e.g. 1M HCl, dioxane or TFA, CH₂Cl₂ or aq. NaOH, THF

Scheme 115: Attempted Synthesis of Naphthol **364**

At this juncture, it was thought that this kind of difficulty would be a common factor for any sort of deprotection of this position, and the sequence that would need to be developed to overcome this would likely result in extensive optimisation for a modest yield and coupled with the already unsatisfactory yields encountered earlier, it was decided that this synthetic sequence was not worth continuing and indeed that this type of system was fundamentally not viable for the types of transformation required for the generation of suitably-functionalised naphthalene aryne precursors and that a different type of system must be developed.

Chapter 6: Results and Discussion - Investigations Into 4-Deoxy Naphthalene Aryne Precursors for Use in the Total Synthesis of Sch 47554 and Sch 4755

Based on the conclusions reached in Chapter 5, a new strategy was explored. The important difference in this strategy is the concept that the third oxygen functionality (on the 4-position) need not be present in the aromatic system at this stage, and can be introduced in the later stages of the total synthesis with suitable oxidation conditions (Scheme 116).



Scheme 116: Conceptual Late-Stage Oxygenation of 4-*des*-hydroxyl Analogue to Desired Quinone

6.1 Synthesis of a Naphthyne Precursor 380

This means that a simplified aryne precursor unit can be envisaged, of the general structure **380**. The lack of an extra oxygen substituent should suppress the tendency to oxidise as the aromatic system in these structures is considerably less electron-rich. With this in mind, the eventual target selected was naphthol **381**. The iodotriflate has already proven in model studies to be effective in the intramolecular aryne-furan Diels-Alder reaction and the synthesis of the similar tosylate should be able to be effected with reasonable and known reactions. In addition, if the iodotriflate is eventually required, its preparation from the tosylate should be uncomplicated.

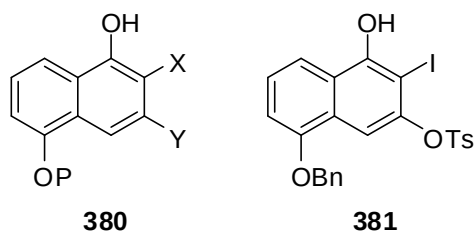
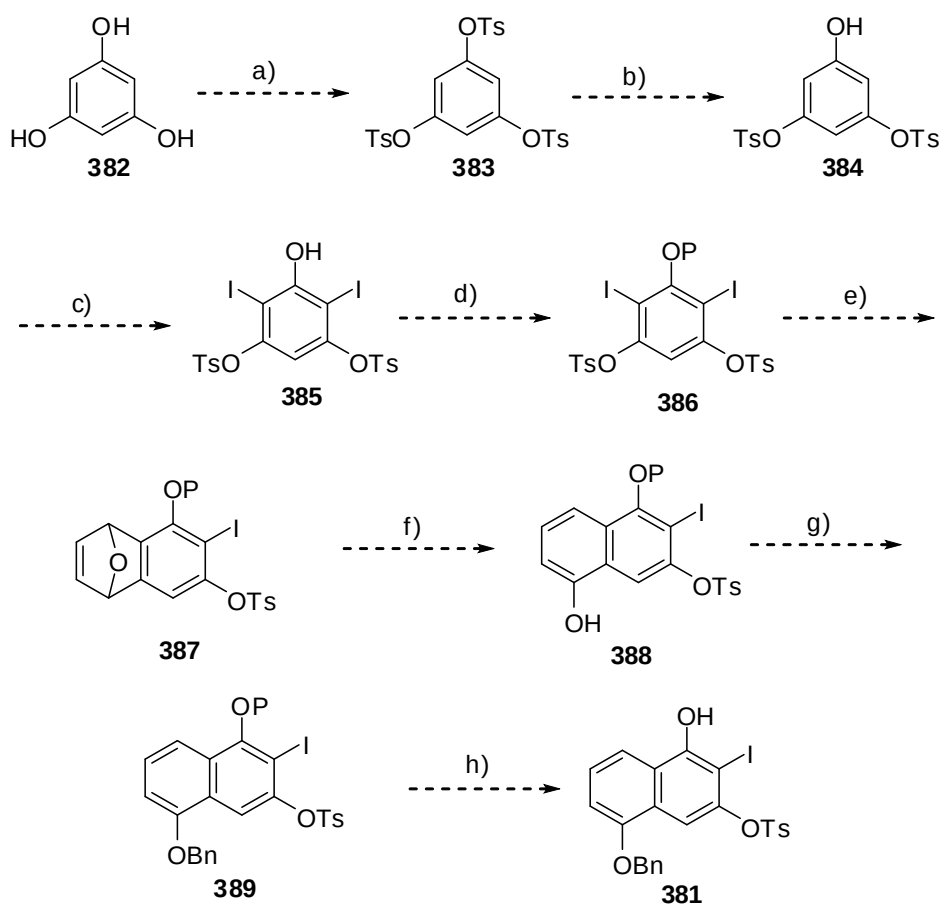


Figure 9: New Target Systems for the Aryne Precursor

The projected synthesis of **381** is shown in Scheme 116. Global tosylation of phloroglucinol, followed by monohydrolysis furnishes phenol **384**, as previously established.¹⁵⁵ It is also previously described that selective bis-*ortho*-iodination of this phenol is possible, to give iodide **385**.¹⁵⁶ Suitable protection then gives a double aryne precursor. The aryne can then be generated by halogen-metal exchange, with subsequent elimination and Diels-Alder reaction with furan to form cycloadduct **387**. Crucially, conditions must be found so that metallation of the aryl group occurs, but the metallated species is stable at that temperature and only collapses upon warming. This is important because the metallated species will be discouraged against further metallation, so the double aryne intermediate will only ever undergo the metallation-elimination-cycloaddition once per molecule. This would not be the case were the cycloadduct formed at low temperatures, as the cycloadduct product is still a perfectly good aryne precursor itself. Once the cycloadduct is formed, it can be aromatised under acidic conditions, giving naphthol **388**, which is protected, desirably as the benzyl ether, before the other oxygen is once again revealed by deprotection to form the naphthol **381**.

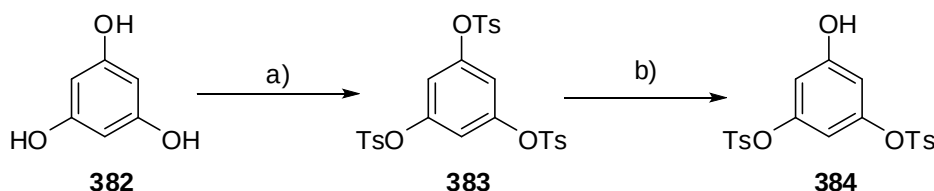


Reagents and conditions: a) TsCl, base; b) KOH, MeOH; c) I^+ source, base; d) protection; e) RLi/RMgCl, furan; f) acid; g) benzylation; h) deprotection

Scheme 117: The Projected Synthesis of Naphthol **381**

Thus the synthesis was initiated with the tosylation of phloroglucinol **382** and subsequent cleavage of one tosyl group under basic conditions in order to form the phenol **384**. Tosylation was originally achieved in an aqueous solution of calcium hydroxide, as described in the original publication,¹⁵⁵ though the insolubility of tosyl chloride, and the product, in water meant that this reaction suffered from inconsistent stirring and was somewhat irreproducible in yields and ease of methodology. Although it is claimed in the same publication that tosylation in pyridine is inadequate, in our hands it was a far more rewarding procedure, with reproducible, near-quantitative yields and so was employed from thereon in. Additionally the reaction is scalable, 250 mmol is the highest scale the reaction was carried out thus far to give the tris-tosylated product **383** in 96% yield (Scheme 118).

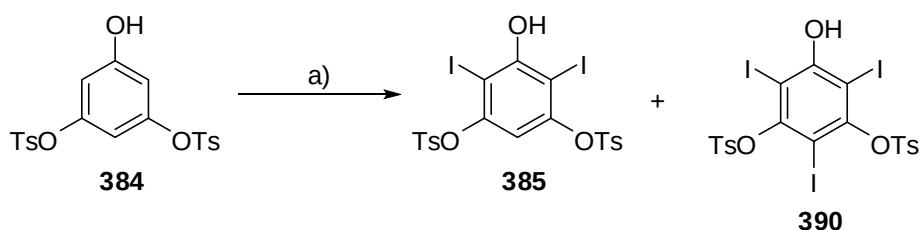
Hydrolysis of **383** with aqueous methanolic potassium hydroxide gave the desired phenol **384**, the reaction proceeds rapidly, though as the starting material is largely insoluble in the solvent system employed, the reaction generally takes longer with scale, but is able to be qualitatively monitored by the extent of dissolution. After isolation and recrystallisation, phenol **384** is obtained in 81% yield.



Reagents and conditions: a) TsCl, C₅H₅N, 96%; b) KOH, H₂O, MeOH, 81%

Scheme 118: Synthesis of Phenol **384**

With phenol **384** in hand, attention was turned to the iodination. Literature precedent¹⁵⁶ indicates that the selective double *ortho*-iodination that is desired is achievable with the use of benzyltrimethylammonium dichloroiodate (Scheme 119).



Reagents and conditions: a) [BnNMe₃][ICl₂], NaHCO₃, CH₂Cl₂ or NIS, CHCl₃, 50°C

Scheme 119: Attempted Synthesis of Diiodide **385**

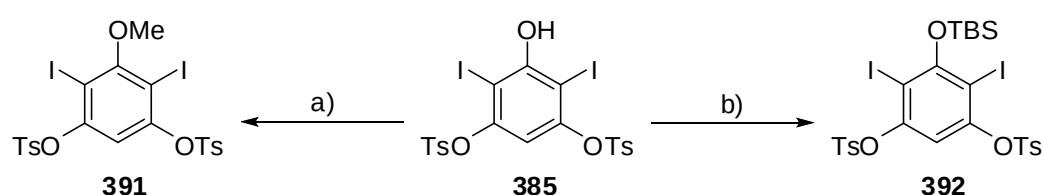
This reaction was repeated and although initially successful, it was discovered that the result was not reproducible and depended upon the batch of iodinating reagent used, with older batches being unusually superior. With newly-purchased reagent, the main product of the reaction mixture was the triiodinated phenol **390**, even with only two equivalents of the reagent. This frustrating result led to the exploration of iodination protocols (Table 11).

Entry	Iodination Reagent(s)	Temperature (/ °C)	Time (/ h)	Ratio of SM	Ratio of diiodo species 385	Ratio of triiodo species 390
1	[BnNMe ₃][ICl ₂]	23	18	0	1	< 0.1
2	[BnNMe ₃][ICl ₂]	23	18	0	<0.1	1
3	NaNO ₂ , I ₂	23	4	1	0.4	<0.05
4	NaNO ₂ , I ₂	23	16	1	0.45	<0.05
5	I ₂ , Cu(OAc) ₂	110	4	-	-	-
6	NIS	40	20	0	1	<0.1
7	ICl, NaHCO ₃	23	18	-	-	-

Table 11: Conditions Examined for Iodination of **384**

It is hard to accurately determine the amount of triiodo compound by ¹H NMR as it has no protons on the main aromatic ring and the resonances for the sulfonate protons are at a virtually identical chemical shift as the diiodo compound. The value for the integration of the resonances from the sulfonate protons with respect to the resonance of the singlet from the diiodophenol is the easiest way to estimate the presence of the triiodophenol: any over-integration to a significant amount is assumed to be from this species. Entries 1 and 2 correspond to different batches of the relevant iodination reagent. The older batch of the dichloroiodate reagent (Entry 1) worked well but was only a small amount remained. The freshly-purchased reagent (Entry 2) gave reproducibly the triiodinated compound. The use of iodine and various activators resulted in little or incomplete reaction (Entries 3-5), and the use of iodine monochloride gave a complex mixture of products (Entry 7). Pleasingly, *N*-iodosuccinimide (NIS) in chloroform at 50 °C (Entry 6) gave a similar result to the successful diiodination previously obtained (Entry 1). Moreover, the reaction was reproducible with different reagent sources and scalable. Recrystallised NIS (from dioxane / diethyl ether, 1:1) was also used, but the yield and purity of the reaction was not significantly improved by this extra-purified reagent. The crude product was purified by trituration or chromatography and diiodophenol **385** was obtained in 65% yield.

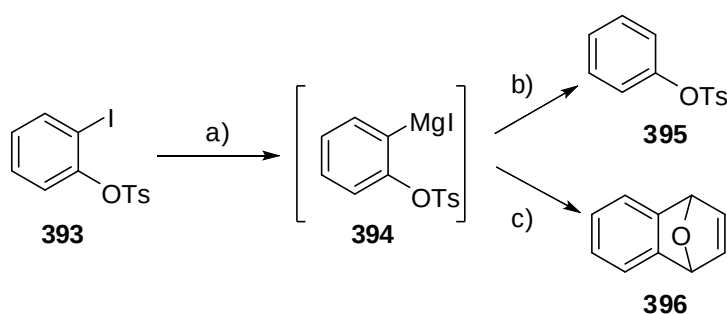
With the synthesis of diiodophenol **385** now established, attention was turned to the next steps. Although methylation would be unsuitable for the synthesis of the desired aryne precursor as it would be impractical to remove, it is a very useful control group upon which to test conditions for the cycloaddition; it has been demonstrated that aryne formation is possible with the methoxy group and it is known to not undergo side-reactions or interfere with the aryne intermediate. Therefore, to this end, the phenol was both methylated and silylated, with the TBS-protected aryne precursor envisaged to be more useful in the synthesis (Scheme 120).



Reagents and conditions: a) Cs_2CO_3 , Me_2SO , Me_2CO , 87% ; b) TBSCl , NEt_3 , CH_2Cl_2 , 86%.

Scheme 120: Functionalisation of Phenol **385**

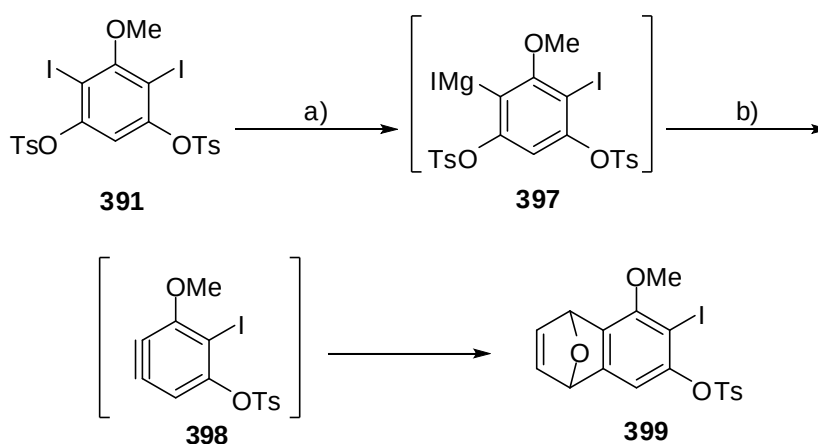
With aryne precursors in hand, investigations into the key cycloaddition reaction could now be undertaken. Initial testing on tosylate **393** indicated that, at least for the isolated *ortho*-iodophenyl tosylate functionality, the use of a Grignard reagent resulted in a successful conversion to the magnesiated derivative, which was quenched with water, demonstrating that it was, crucially, stable at $-78\text{ }^\circ\text{C}$ (*cf.* the lithiated equivalent, which is known to eliminate at this temperature when tosylate is the leaving group). Upon warming in the presence of furan, the desired cycloadduct **396** was formed in high yield, indicating that the species readily eliminates under these conditions (Scheme 121).



Reagents and conditions: a) *i*-PrMgCl, THF, $-78\text{ }^{\circ}\text{C}$; b) H_2O , 90% (crude); c) furan, $-78\text{ }^{\circ}\text{C}$ to $25\text{ }^{\circ}\text{C}$, 85%.

Scheme 121: Magnesiumation and Aryne Formation from **393**

Attention was then turned to the double aryne precursors. The reactivity of the methoxy analogue **391** was initially examined (Scheme 122). Treatment with *iso*-propylmagnesium chloride, as before, led to a magnesiated species **397**, the presence of which could be inferred using an aqueous quench. Upon warming in the presence of furan, two main products were observed. The first was the deiodinated starting material (though no doubly deiodinated material was observed) and the second product corresponded to the desired cycloadduct **399**, which was isolated in 42% yield.

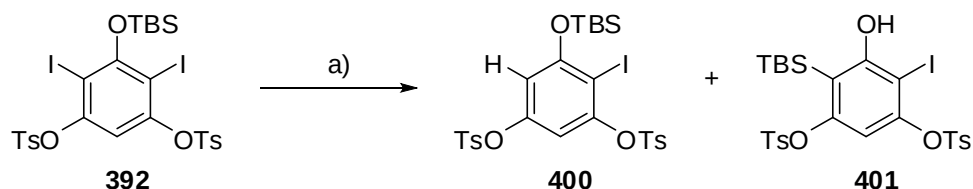


Reagents and conditions: a): *i*-PrMgCl, THF, $-78\text{ }^{\circ}\text{C}$; b) furan, $-78\text{ }^{\circ}\text{C}$ to rt, 42%

Scheme 122: Aryne Generation from **391** and Subsequent Cycloaddition to Form Cycloadduct **399**

The result was encouraging in that the desired cycloadduct was obtained, though the yield was modest. However, the use of a synthetically applicable protecting group was of more importance and the reaction was therefore developed with other analogues.

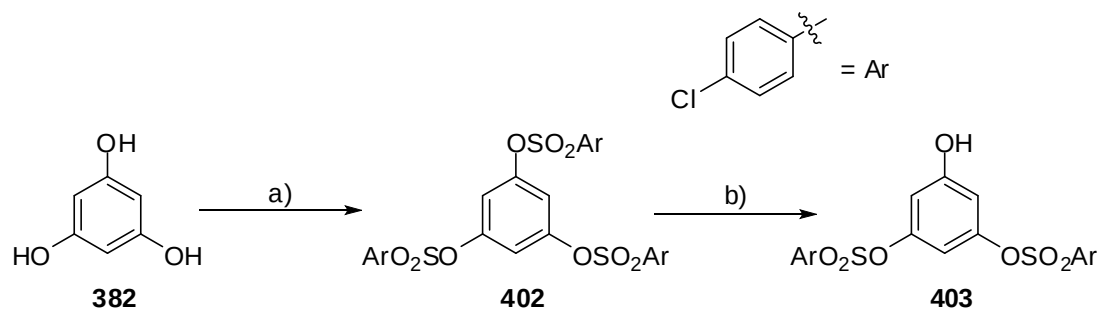
Under the same conditions for aryne formation, the silyl ether analogue **392** gave two major products, which were identified as the deiodinated starting material **400** and another species which was assigned as the product of an *O* to *C* migration of the TBS group, resulting in *ortho*-silylated phenol **401** (Scheme 123). No cycloadduct was observed; it is clear that the migration of silicon is faster than elimination.



Reagents and conditions: a) *i*-PrMgCl, THF, -78°C ; b) furan, -78°C to rt

Scheme 123: Reactivity of Silyl Ether **392** under Aryne-Forming Conditions

One possible reason for the modest yield for the cycloaddition is that the elimination step is slow, and the use of a better leaving group could be advantageous. It has been shown⁷⁷ that the *para*-chlorobenzenesulfonate is a better leaving group than tosylate under similar conditions to those employed here. Therefore, it is expected that the use of this leaving group would effect aryne formation at lower temperature and at a quicker rate. Therefore the synthesis of the *p*-chlorobenzenesulfonate analogue was undertaken. The phenol **403** was synthesised using the same conditions as the tosylate analogue (Scheme 124).

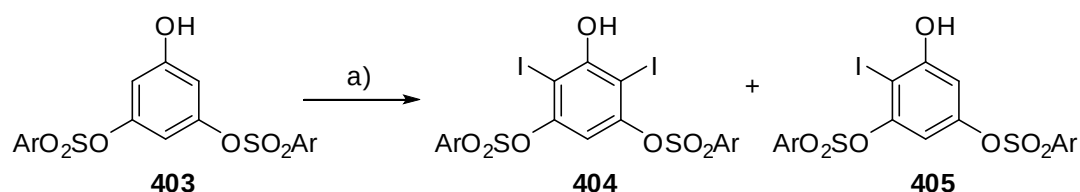


Reagents and conditions: a) *p*-ClC₆H₄SO₂Cl, C₅H₅N, 88%; b) KOH, H₂O, MeOH, 75%

Scheme 124: Synthesis of Phenol **403** from **382**

The problems of the iodination step documented previously also applied to the iodination of **403**. The use of the dichloroiodate gave overiodination as before. Unfortunately, the conditions discovered using NIS that successfully gave the

diiodotosylate were not successful with **403** as the substrate. The reaction did not go to completion, even after 48 hours, though a quantity of starting material was consumed. NMR indicates that there is little or no over-iodination and instead a mixture of starting material, monoiodinated product and diiodinated product. Therefore, other iodination conditions were examined in order to obtain the desired diiodide product **404** in high yield (Scheme 125).



Reagents and conditions: a) see Table 12

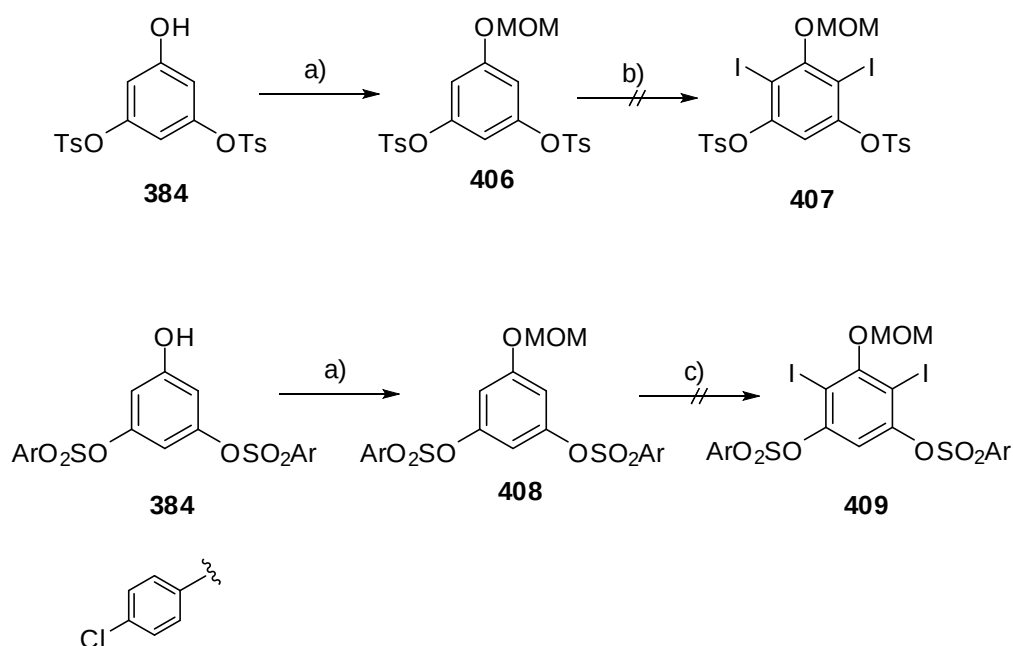
Scheme 125: Conditions Examined for Iodination of **403**

Entry	Iodinating Agent	Temperature (/ °C)	Time (/ h)	Result
1	2.1 eq. NIS	40	20	Mainly starting material 403
2	2.1 eq. NIS	40	48	Small amount of 404 , mainly monoiodide 405
3	2.1 eq. NIS	60	20	Complex mixture
4	4.0 eq. NIS	40	20	Overiodination and complex mixture.
5	3 eq. I ₂ , NaNO ₂	80	24	Mainly starting material 403
6	3 eq. [BnNMe ₃][ICl ₂]	25	14	Complex mixture
7	2.0 eq. I ₂ , AgO ₂ CCF ₃	25	10	Mixture of monoiodide 405 and diiodide 404
8	2.5 eq. I ₂ , AgO ₂ CCF ₃	25	22	Mainly diiodide 404

Table 12: Selected Conditions Examined in the Diiodination of Phenol **403**

Iodine with sodium nitrite as an activator failed to return any iodinated product even after prolonged reaction times and increased equivalents (Entry 1). Benzyltrimethylammonium dichloroiodate (Entry 6) or iodine monochloride both gave a complex mixture of uncharacterisable products, but using iodine with silver trifluoroacetate as an activator a mixture of mono-iodinated and diiodinated products was recovered (Entry 7). Further optimisation of the reaction (using 2.5 equivalents of both iodine and silver trifluoroacetate) led to the diiodide **404** as the only major product of the reaction (Entry 8).

Alternatively, a route where protection occurred before iodination was also examined, in order to determine whether this sequence would confer a higher yield or greater regioselectivity of the iodination in the reaction sequence. Accordingly, the methoxymethyl (MOM) ethers **406** and **408** were synthesised and then iodinated under the same conditions (Scheme 126).

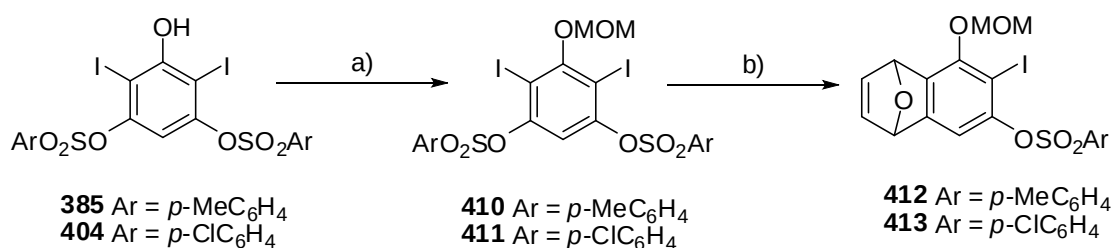


Reagents and conditions: a) *i*-Pr₂NEt, MOMCl, CH₂Cl₂, **406**, 81%, **408** 79%; b) I₂, AgO₂CCF₃, CHCl₃, 40 °C; c) I₂, AgO₂CCF₃, CHCl₃.

Scheme 126: Attempted Protection-Iodination Route to Diiodoethers **406** and **408**

Unfortunately, under all iodination conditions tried, mixtures of compounds were obtained, with either of the bis-sulfonates **406** and **408**. In many cases, the di-*ortho*-iodonated product was either not present or in negligibly low proportion of products, as judged by ^1H NMR. It seems evident that the protection of the phenol reduced, not enhanced, the regioselectivity of the iodination. Therefore this route was not investigated further and the original iodination protocol was used to prepare the diiodophenols **385** and **404** and protection undertaken afterwards.

With the diiodophenols in hand, the next variable to be examined was the protecting group to be used, in light of the instability of the TBS ether **392** under the reaction conditions used to form the aryne. The next protecting group to be investigated was the methoxymethyl (MOM) group, a group known for its *ortho*-directing ability, stability to the conditions of aryne formation but easily removed under acidic conditions. The corresponding MOM ethers **410** and **411** were thus synthesised from the phenols with methyl chloromethyl ether and Hünig's base, and their reactivity when subjected to the cycloaddition conditions was examined (Scheme 127). Some of the variables were investigated in the aryne-generation/cycloaddition sequence with the intent of optimising the reaction. Firstly the organometallic species used to generate the aryne precursor was varied; both *iso*-propylmagnesium chloride and *n*-butyllithium were used. In addition, the temperature and rate of warming were varied and these conditions were explored on aryne precursors containing both tosylates and *para*-chlorobenzenesulfonates (Table 13).



Reagents and conditions: a) *i*-Pr₂NEt, MOM-Cl, CH₂Cl₂, **410**: 83%, **411**: 81%; b) see Table 13.

Scheme 127: The Synthesis of Ethers **410** and **411** and Conversion to Cycloadducts **412** and **413**

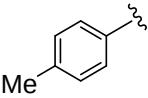
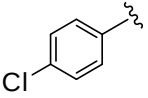
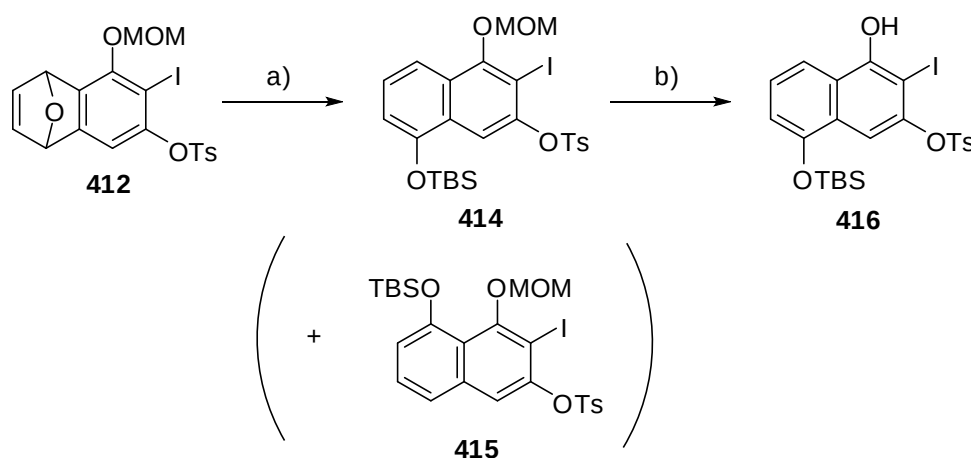
Entry	Conditions	Result	Result
		Ar = 	Ar = 
1	i) <i>i</i> -PrMgCl, THF, -78 °C, ii) furan, -78 °C to rt slowly	42%, pure	<10% impure
2	i) <i>i</i> -PrMgCl, THF, -78 °C, ii) furan, -78 °C to rt rapidly	55%, pure	<10% impure
3	i) <i>n</i> -BuLi, THF, furan, -78 °C, ii) 78 °C to rt slowly	50%, slightly impure	Uncharacterisable mixture
4	i) <i>n</i> -BuLi, THF, furan, -78 °C, ii) 78 °C to rt rapidly	51%, somewhat impure	Not run
5	i) <i>i</i> -PrMgCl, THF, -78 °C, ii) furan, -78 °C to reflux	22%, slightly impure	Not run

Table 13: Conversion of Ethers **410** and **411** into Cycloadducts **412** and **413** Respectively

Table 13 indicates that under all conditions examined the tosylate **410** yielded the desired cycloadduct **412** to some extent, but was sensitive to the conditions employed. The optimal result was achieved with *iso*-propylmagnesium chloride, when warming to ambient temperature rapidly and stirring for 18 hours after being stirred at -78 °C for one hour (Entry 2). The use of butyllithium to generate the aryne was successful, giving comparable yields but with greater amounts of impurities (Entry 3) and so was not used further. Under all conditions employed, the *para*-chlorobenzenesulfonate-based aryne precursor **411** did not deliver the desired cycloadduct **413**. The reason for its use was its presumed superior leaving group ability, but it appears that it may be so facile to induce it to leave that it is uncontrollable. Analysis of the product mixture yields no identifiable structures and indicates a complex mixture of decomposition products, even when furan is present in the reaction mixture from the start. Therefore it was concluded that the MOM-protected diiodotosylate was the best substrate for the cycloaddition.

The advantage of the MOM-group is that it promotes halogen-metal exchange in the cycloaddition step, but it is inconvenient in the cycloadduct-opening step as it is sensitive to the acidic conditions normally employed. Therefore, milder conditions were sought for aromatisation. It has been shown¹⁵⁷ that a mixture of *tert*-butyldimethylsilyl triflate and 2,6-lutidine is able to open cycloadducts, delivering the TBS-protected naphthol. Although the free naphthol is desirable in order to attach the saccharide unit, this silyl ether will be useful as a model, and it should be simple enough to deprotect, if required.

Thus, the aromatisation was examined employing these reagents, and the desired silyl ether **414** was isolated in 53% yield. The moderate yield is explained by the lack of regioselectivity of the aromatisation, as the major by-product is the opened *syn*-product **415**. This is presumably because the mechanism does not involve a carbocation that can be stabilised by the other substituents, as detailed earlier in Scheme 49, and so the influence of the oxygen in the tosylate group does not direct the aromatisation and an almost 1:1 mixture is obtained. The synthesis of a model naphthol for the investigation into the key intramolecular aryne-furan cycloaddition was then achieved with the deprotection of the MOM group with trifluoroacetic acid to yield naphthol **416** in reasonable yield (Scheme 128). Combination with an appropriate silicon linker and a model furan can be now be undertaken, currently elsewhere in the group.

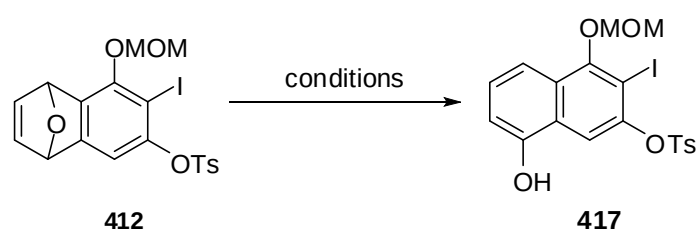


Reagents and conditions: a) TBS-OTf, 2,6-lutidine, CH₂Cl₂, 53%; b) TFA, CH₂Cl₂, 76%.

Scheme 128: The Conversion of Cycloadduct **412** into Naphthol **416**

6.2 Use of 4-Deoxy Naphthynes Precursors in Studies Towards the Synthesis of Sch 47554 and Sch 4755

Providing a route directly to the naphthol **417** is desirable, as the focus is now on making a system that is applicable to the real synthesis of the target molecule. Procedures were then explored in order to generate the naphthol **417** instead of the silyl ether **414** (Scheme 129). Protic acids were ruled out but some mild Lewis acids were examined in order to effect aromatisation (Table 14).



Reagents and conditions: a) see Table 14.

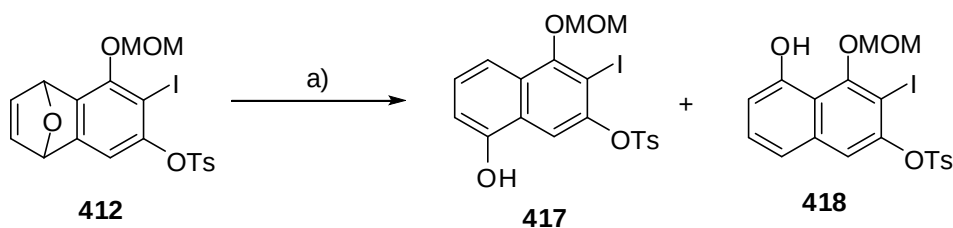
Scheme 129: The Aromatisation of Cycloadduct **414**

Entry	Conditions	Result
1	ZnCl ₂ (1.0 M in Et ₂ O), CH ₂ Cl ₂	Starting material
2	Me ₂ AlCl, CH ₂ Cl ₂ , -78 °C	Starting material
3	MeAlCl ₂ , CH ₂ Cl ₂ , -78 °C	Starting material
4	Me ₂ AlCl, CH ₂ Cl ₂ , rt	No identifiable products
5	MeAlCl ₂ , CH ₂ Cl ₂ , rt	No identifiable products
6	Cp*Ru(cod)Cl, DCE, 80 °C, 0.5 h	No starting material remaining and no identifiable products
7	RuCl ₂ (CO) ₃ , DCE, 80 °C, 18 h	No starting material remaining and no identifiable products
8	2,6-lutidine, TMS-OTf, CH ₂ Cl ₂ , rt, 3 h	417 (in variable yields, 50-61%)

Table 14: Conditions Employed in Aromatisation of Cycloadduct **417**

Zinc chloride solution was first examined, but even with prolonged reaction time and in vast excess the zinc chloride neither aromatised the cycloadduct nor cleaved the MOM group; only starting material was recovered (Entry 1). Dimethylaluminium chloride and methylaluminium dichloride were also examined. At $-78\text{ }^{\circ}\text{C}$, neither Lewis acid instigated any reaction, even when allowed to react for six hours (Entries 2 and 3). At $0\text{ }^{\circ}\text{C}$, after two hours, although the starting material had largely disappeared, the product was a complex mixture by ^1H NMR and clearly too reactive at this temperature (Entries 4 and 5).

Use of either ruthenium catalyst previously described ($\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$ ¹⁵⁸ or $\text{RuCl}_2(\text{CO})_3$ ¹⁵⁹) as successful for opening simple cycloadducts did not achieve the desired transformation. In both cases, a complex mixture of uncharacterisable products was obtained, with many possible side reactions, including deprotection of the methoxymethyl group or ruthenium insertion into the carbon-iodine bond. However, using trimethylsilyl triflate with 2,6-lutidine, analogously to the conditions described with *tert*-butyldimethylsilyl triflate earlier, enabled the formation of the desired naphthol **417**. Extended reaction times lead to cleavage of the methoxymethyl group and a higher level of impurities. It is again relevant that the aromatisation does not proceed *via* a carbocation intermediate and so is formed without regioselectivity as described previously, giving the two regioisomeric naphthols **417** and **418**. The desired naphthol **417** was isolated in yields of 54% and the undesired naphthol **418** was only recoverable impure.

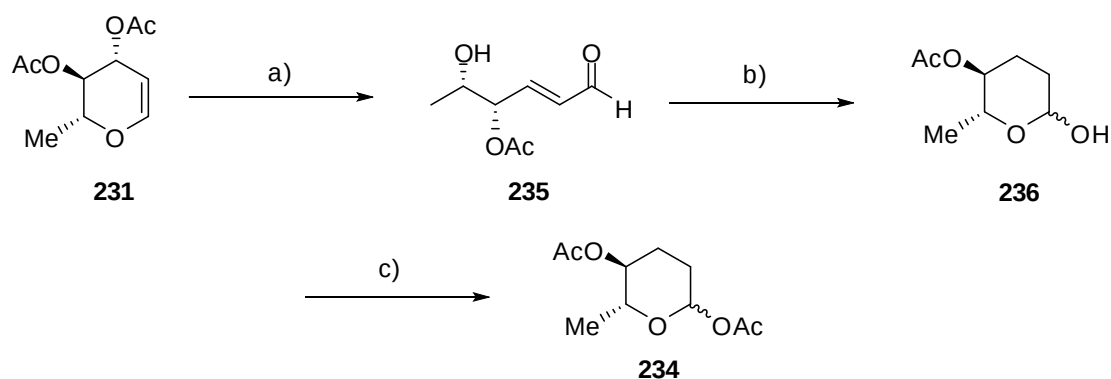


Reagents and conditions: a) TMS-OTf, 2,6-lutidine, CH_2Cl_2 , **417**: 54%

Scheme 130: The Conversion of Cycloadduct **412** into Naphthols **417** and **418**

6.3 Synthesis of Suitable Glycosyl Donors for C-Aryl Glycosidation

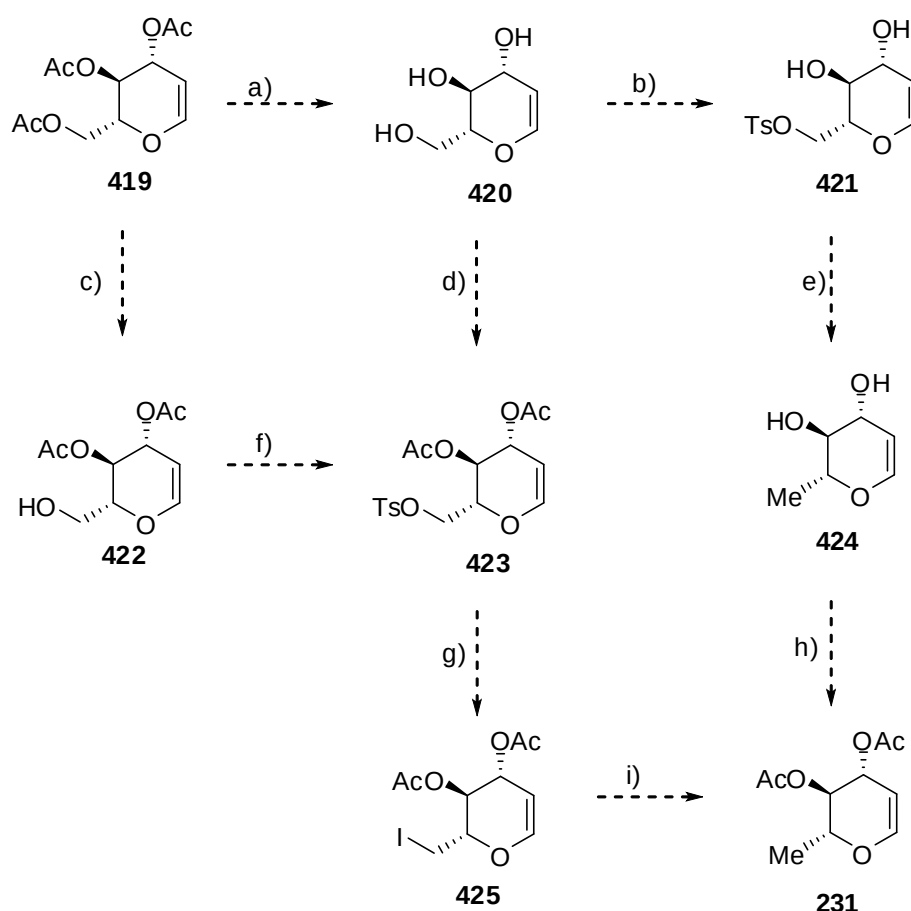
With a naphthol that can be glycosidated, attention was now turned to the synthesis of the sugar unit required in the synthesis of the target molecule. As described in Section 4.2.2, work has already been carried out in the group on an advanced model system using the enantiomer of the sugar unit found in Sch 47554 and Sch 47555 in order to simplify the synthesis and to develop the methodology. However, all work now is intended to be used directly on the synthesis of the target molecules and so only the correct enantiomer for this target will be used. The required donor for the C-glycosidation is acetate **234**, which can be reached, in transformations previously described in the group,¹³⁹ from glycal **231** (Scheme 131).



Reagents and conditions: a) H₂O, 80 °C, 98% (crude); b) H₂, Pd/C, EtOH, 75%; c) Ac₂O, C₅H₅N, CH₂Cl₂, 85%.

Scheme 131: Conversion of the Glycal **231** to the Glycosyl Acetate **234**

The enantiomer of **231** is commercially available, but not **231** itself and so a viable synthetic route to **231** was developed. Possible routes from tri-*O*-acetyl D-glucal, **419**, were investigated in parallel (Scheme 132). All transformations detailed are either previously described or are trivial procedures.



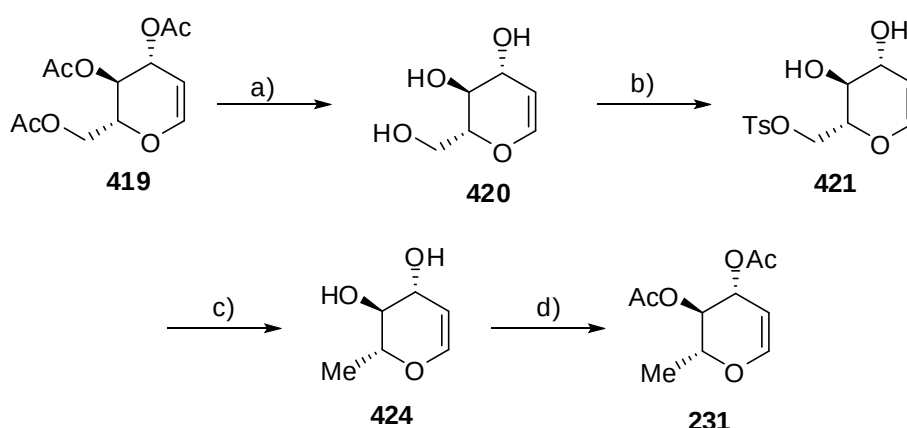
Reagents and conditions: a) K_2CO_3 , MeOH; b) TsCl, $\text{C}_5\text{H}_5\text{N}$; c) lipase, pH 7 buffer; d) i) TsCl, $\text{C}_5\text{H}_5\text{N}$, ii) Ac_2O ; e) LiAlH_4 , Δ ; f) TsCl, $\text{C}_5\text{H}_5\text{N}$; g) NaI, Δ ; h) Ac_2O , $\text{C}_5\text{H}_5\text{N}$; i) Bu_3SnH , AIBN, Δ .

Scheme 132: Routes to Glucal **419** from Glycal **231**

The first route entails global deacetylation to give D-glucal, **420**. This is selectively tosylated at the primary hydroxyl group to give tosylate **421**. This can be reduced (via the dianion) to D-rhamnal (**424**),¹⁶⁰ which can then be acetylated to give the desired sugar **231**.

A second route is also described. The key intermediate in this route is tosylate **423**, which could be obtained in one of two ways, either by enzymatic deacetylation,¹⁶¹ selective for the primary position and then tosylation of the revealed primary hydroxyl group or by global deacetylation and selective primary tosylation, as before, with subsequent acetylation.¹⁶² Subsequently, tosylate **423** could be converted into the corresponding iodide **425** and then radical dehalogenation with tributyltin hydride delivers the protected rhamnal **231**.¹⁶²

The former route was examined first, as it has the advantage of fewer steps and requiring no purification until rhamnal **424**. Global deacetylation and selective primary tosylation was facile and the crude tosylate **421** was subjected to direct reduction with lithium aluminium hydride. This procedure gives the desired product **424** in moderate yield on a small-medium scale (48% on a 50 mmol scale), but the yield dropped on a larger scale (28-36% on 50-150 mmol scale). The diol could then be acetylated in 98% yield under standard conditions to deliver the desired intermediate **231** (Scheme 133).



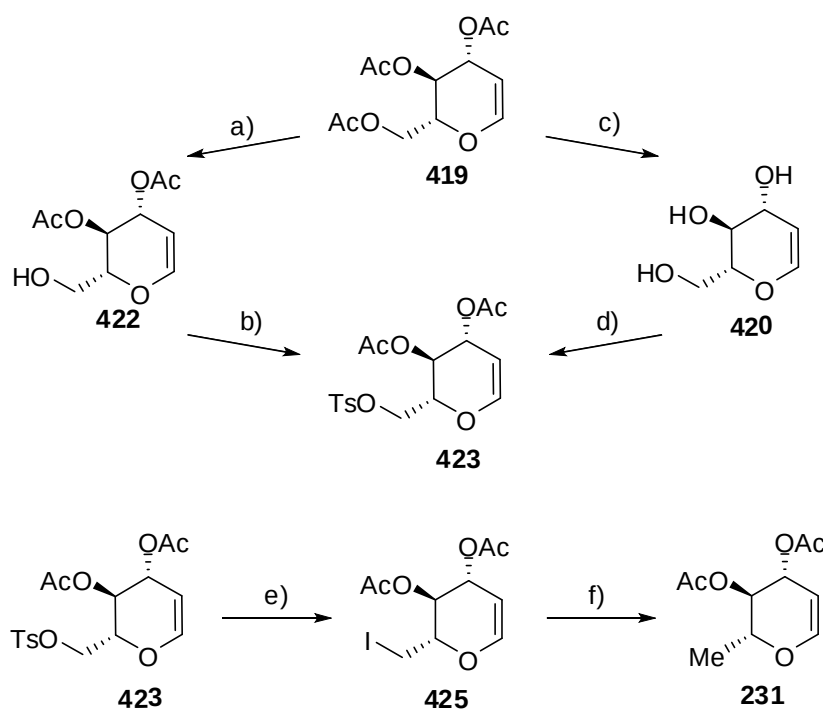
Reagents and conditions: a) K_2CO_3 , MeOH, quant. (crude) ; b) TsCl, $\text{C}_5\text{H}_5\text{N}$, CH_2Cl_2 , 82% (crude) ; c) LiAlH_4 , Δ , 48%; d) Ac_2O , $\text{C}_5\text{H}_5\text{N}$, CH_2Cl_2 , 98%.

Scheme 133: Synthesis of Rhamnal **231** from Glucal **419**

The reduction step of this sequence is unsatisfactory, as scaling up decreases yield and becomes increasingly more hazardous and time-consuming as the LAH solution must still be added and quenched dropwise. Therefore, the alternative routes were examined.

In the second general route, key intermediate **231** was synthesised from tosylate **423** by displacement of the tosylate with iodide and then radical dehalogenation replacing iodine with hydrogen. Tosylate **423** itself can be obtained in one of two ways, either by enzymatic deacetylation selective for the primary acetate functionality and tosylation of the resulting hydroxyl functionality or global deacetylation and selective primary tosylation, as in the previous route and one-pot acetylation of the remaining hydroxyl functionalities. Both routes were successful, though the latter gave an

overall better yield (72% compared to 65%) and was more practical on larger scales so was used in future synthesis. Tosylate **423** was then converted into iodide **425** in 91% yield, which was subsequently dehalogenated with tributyltin hydride and radical initiator 1,1'-azobis(cyclohexanecarbonitrile) (ABCN) to give protected rhamnal **231** in 98% yield (Scheme 134).

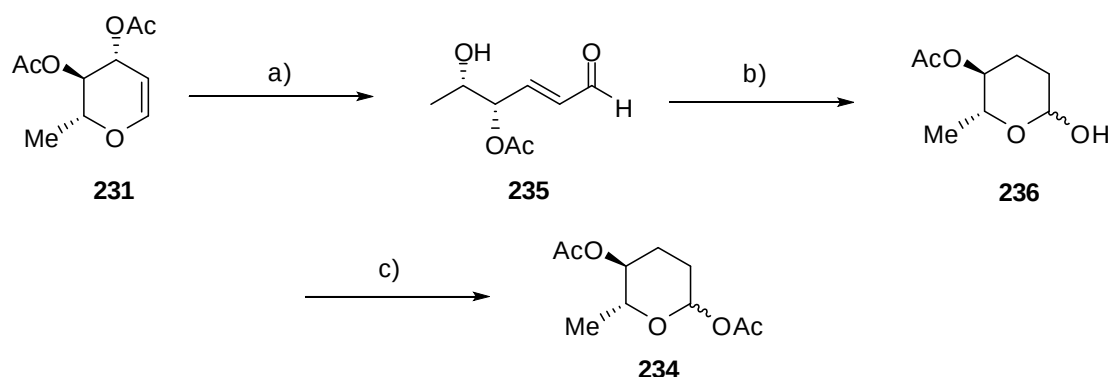


Reagents and conditions: a) CCL lipase, pH 7 buffer, Me₂CO, *i*-Pr₂O, 78%; b) TsCl, C₅H₅N, 84%; c) K₂CO₃, MeOH, quant. (crude); d) i) TsCl, C₅H₅N, ii) Ac₂O, 72%; e) NaI, *i*-BuCOMe, Δ, 91%; f) Bu₃SnH, ABCN, PhMe, Δ, 98%

Scheme 134: Alternative Routes to Diacetate **231**

This route was also undertaken successfully, and although containing an extra step gave a much better yield of **231**, 64% overall from **419** (*cf.* 39% for the route involving LAH reduction).

With rhamnal **231** in hand, the conversion to glycosyl donor **234** was undertaken. Heating in water at 80 °C gave the *E*-alkene **235**¹⁶³ *via* a Ferrier-type rearrangement. Aldehyde **235** could be hydrogenated with palladium on carbon to give lactol **236**, in 71% yield from **231**, which could be converted to acetate **234** in 84% yield (Scheme 135).

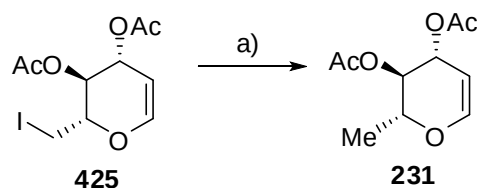


Reagents and conditions: a) H_2O , 80 °C; b) H_2 , Pd/C, EtOH, 71% (over 2 steps); c) Ac_2O , $\text{C}_5\text{H}_5\text{N}$, CH_2Cl_2 , 84%

Scheme 135: Synthesis of Glycosyl Donor **236**

It was noted that the hydrogenation step was only successful with rhamnal **424** synthesised from the LAH reduction route; when a batch synthesised from iodide **425** was used the hydrogenation gave incomplete reaction and a complicated array of products. It was hypothesised that there were trace tin residues which were poisoning the palladium catalyst in the hydrogenation, so more careful chromatography was undertaken, including using a 10% KF in silica column, however the problem persisted. As this route was more practical and significantly better yielding, it was of greater desire to try and find an alternative way to effect this transformation without tin rather than to use the other route on large scale.

Accordingly, other conditions were examined for the dehalogenation. The use of sodium cyanoborohydride as a stoichiometric reductant with catalytic (10 mol%) tributyltin chloride¹⁶⁴ was examined, with the hope that using one-tenth the amount of tin would be sufficient to suppress this presumed poisoning. Also investigated were the use of alternative, tin free procedures, one in which tris(trimethylsilyl)silane is used as the radical source¹⁶⁵ and one which exploits a palladium-mediated hydride transfer.¹⁶⁶



Reagents and conditions: a) see Table 15

Scheme 136: Alternative Dehalogenation Reactions of Iodide **425**

Entry	Reagents	Temperature (/ °C)	Time (/ h)	Yield of 231 (/ %)	Comments
1	Bu ₃ SnCl (10 mol%), 2 eq. NaBH ₃ (CN), ABCN, <i>t</i> -BuOH	80	4-12 ^a	71	Product slightly impure after chromatography
2	(SiMe ₃) ₃ SiH, ABCN, PhMe	110	3	91	Yield decreases with aged reagent
3	Pd/C, H ₂ , NEt ₃ MeOH	23	3	52	Slow addition of NEt ₃ required

^aSmall amount of starting material still present (by TLC analysis) after 4 hours, but still present after 12 hours, extended reaction times have no effect in separate experiment

Table 15: Alternative Dehalogenation Reactions of Iodide **425**

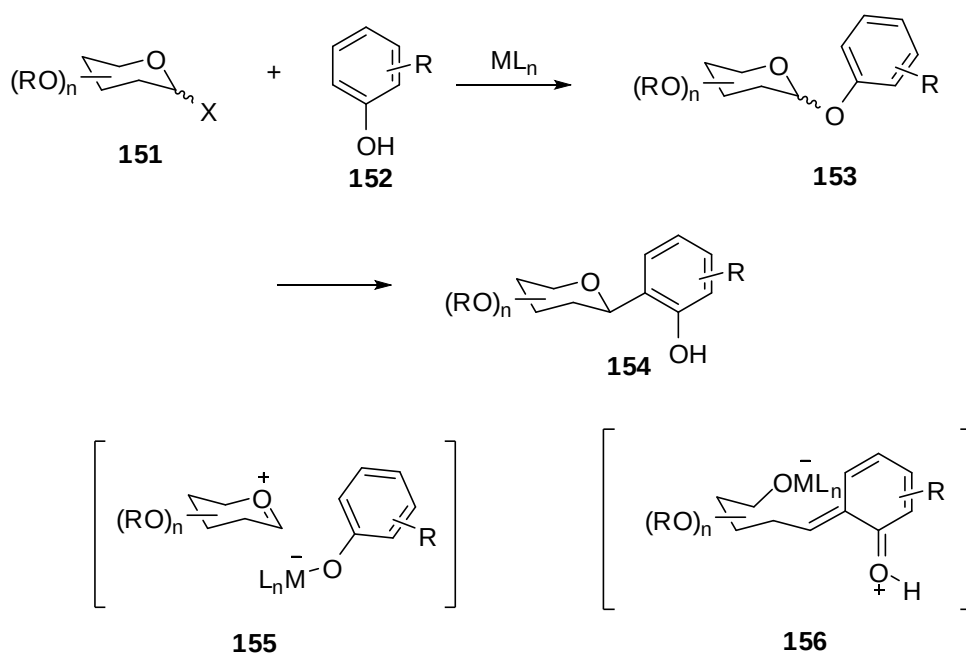
As is evident from Table 15, all three sets of conditions assessed gave the desired product **231** in various yields. Using sodium cyanoborohydride and catalytic tributyltin chloride (Entry 1), the reaction went near to completion, but starting material was still present and the isolated yield of the product was notably lower than the original tin-mediated reaction. The presence of trace tin residues is also still a threat with these conditions. In contrast, the tris(trimethylsilyl)silane-mediated reaction (Entry 2) proceeded in a straightforward, high-yielding manner, giving the product pure of silicon-based by-products, according to ¹H NMR. Although it has already been noted that concentrations of residues undetectable by NMR can cause problems, it is envisaged that the silicon by-products will not interfere in the hydrogenation as the tin-based ones do. The palladium-mediated dehalogenation proceeded in moderate yield, presumably due to extensive side-product formation,

e.g. the product arising from hydrogenation of the alkene functionality. With these results, the silicon-mediated radical dehalogenation was used in future experiments in the synthesis of rhamnal **231**.

6.4 Studies into the Synthesis of Glycosyl Acetates and Naphthols for Use in the C-Aryl Glycosidation in the Synthesis of Sch 47554 and Sch 47555

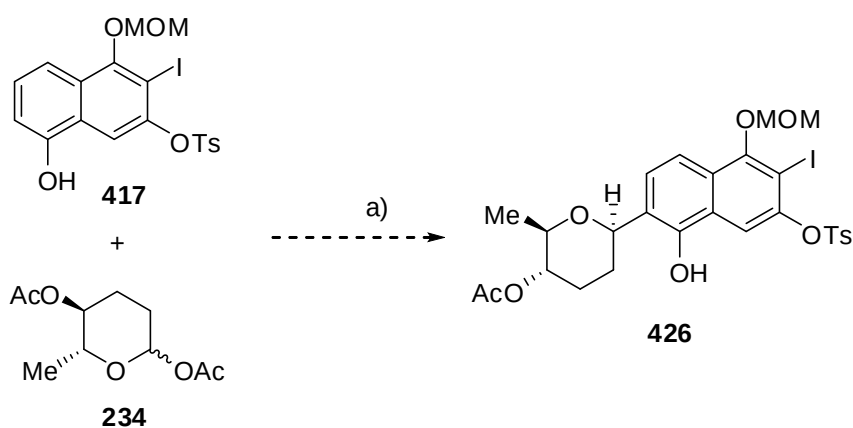
With a robust route to glycosyl acetate **234** and the synthesis of a suitable naphthol **417**, attention could then be turned to the formation of a key carbon-carbon bond *via* an aryl C-glycosidation.

Recalling Scheme 33 from Section 3.1 the desired aryl C-glycoside can be obtained from combining acetate **151** and naphthol **152** in the presence of a suitable Lewis acid (and, where appropriate, an activator and/or dehydrating agent). Initially, the *O*-glycoside is formed at low temperatures, but upon warming the glycosyl moiety can be transferred to the carbon centre via a Friedel-Crafts-type coupling between the ion pair **155**. The *O*-glycoside formation is reversible, whereas the formation of the *C*-glycoside is irreversible and is regioselective for the *ortho*-position, a notable feature of this reaction. The desired β -anomer is thermodynamically favoured and the initial kinetic ratio can be equilibrated through the *ortho*-quinone methide species **156** (Scheme 137). The Lewis acid employed must therefore be capable of promoting this sequence of reactions.



Scheme 137: Mechanistic Aspects of the Lewis Acid-Promoted C-Aryl Glycosidation

In Section 3.1, this work is described with the hafnocene dichloride/silver perchlorate Lewis acid combination, so this system was examined for the synthesis of C-aryl glycoside **426** from **417** and **234**. Additionally, other Lewis acids known to effect C-aryl glycosidation were examined (Scheme 138, Table 16).



Reagents and conditions: a) see Table 16

Scheme 138: The Desired C-Aryl Glycosidation of Glycosyl Acetate **234** with Naphthol **417**

Entry	Lewis Acid	Additive	Solvent	Temperature (/°C)	Result
1	Cp ₂ HfCl ₂	AgClO ₄ , 4Å MS	CH ₂ Cl ₂	–78 to 23	<10% recovered 417
2	BF ₃ ·OEt ₂	4Å MS	CH ₂ Cl ₂	–78 to 23	-
3	TMS-OTf	-	MeCN	0 to 23	<10% recovered 417
4	TMS-OTf	AgClO ₄	MeCN	0 to 23	-

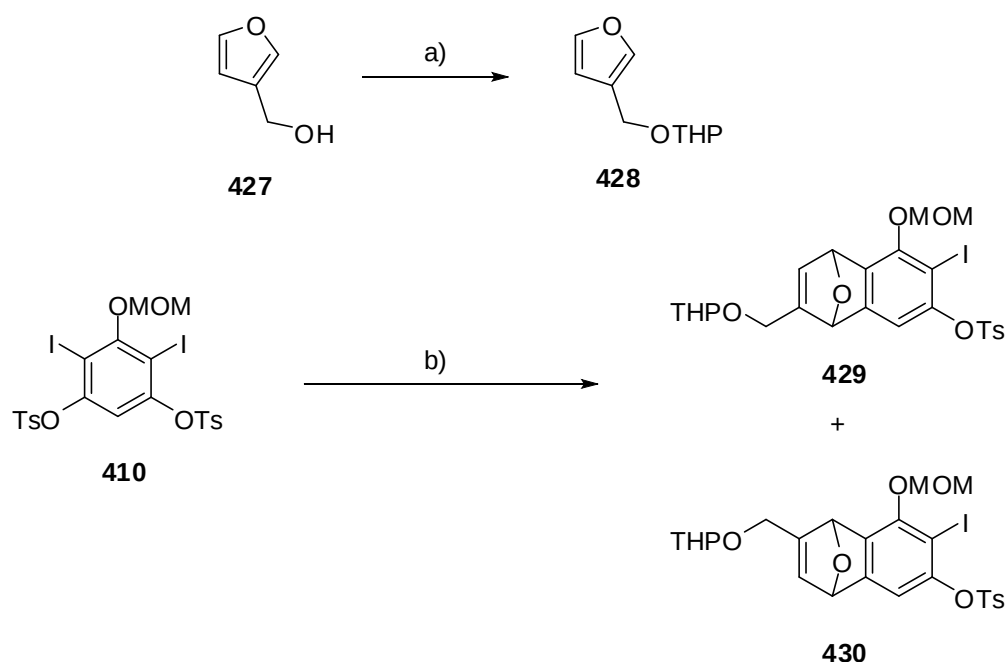
Table 16: Reaction Conditions Examined for C-Aryl Glycosidation of Naphthol **417**

It was established with the development of the C-aryl glycosidation that the optimal ratio of acceptor to donor is 2:1, so this ratio of naphthol **417** to acetate **234** was used in all reactions. However, as can be seen from Table 16, all systems tried failed to yield detectable amounts of desired C-glycoside **426** and furthermore, very little recovery of naphthol **417** was achieved.

Simultaneously, another disconnection was being explored in which the aryne generated from the diiodotosylate was allowed to react with a 3-glycosylfuran, the product of which, if regioselectively formed, could be aromatised to give the same species thus obviating the need for a glycosidation reaction. A similar reaction was met with little success in earlier systems¹³⁹ but it was felt that with the different steric and electronic properties of the aryne precursor, examining this aryne precursor with model furans would be worthwhile.

The tetrahydropyran ether **428**, envisaged as an adequate model for a 3-glycosylfuran, was synthesised in one step from commercially available furan **427**. This furan was then subjected to the relevant aryne derived from **410**, with two possible regioisomers **429** and **430** anticipated. Although the reaction proceeded in moderate yield, neither regioisomer was favoured; they were formed in a 1:1 ratio and were

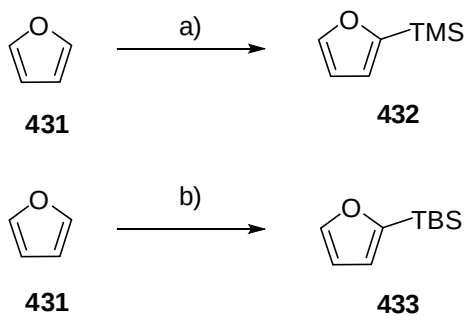
chromatographically inseparable (Scheme 139), indicating that this type of methodology would not be applicable for this type of aryne precursor.



Reagents and conditions: a) DHP, *p*-TsOH, CH₂Cl₂, 78 %; b) *i*-PrMgCl, 2 equiv. **428**, THF, -78 °C to rt, 38% (inseparable 1:1 mixture of **429** and **430**)

Scheme 139: Synthesis of Furan **428** and an Attempted Regioselective Aryne-Furan Diels-Alder Reaction Between **428** and the Aryne Derived from **410**

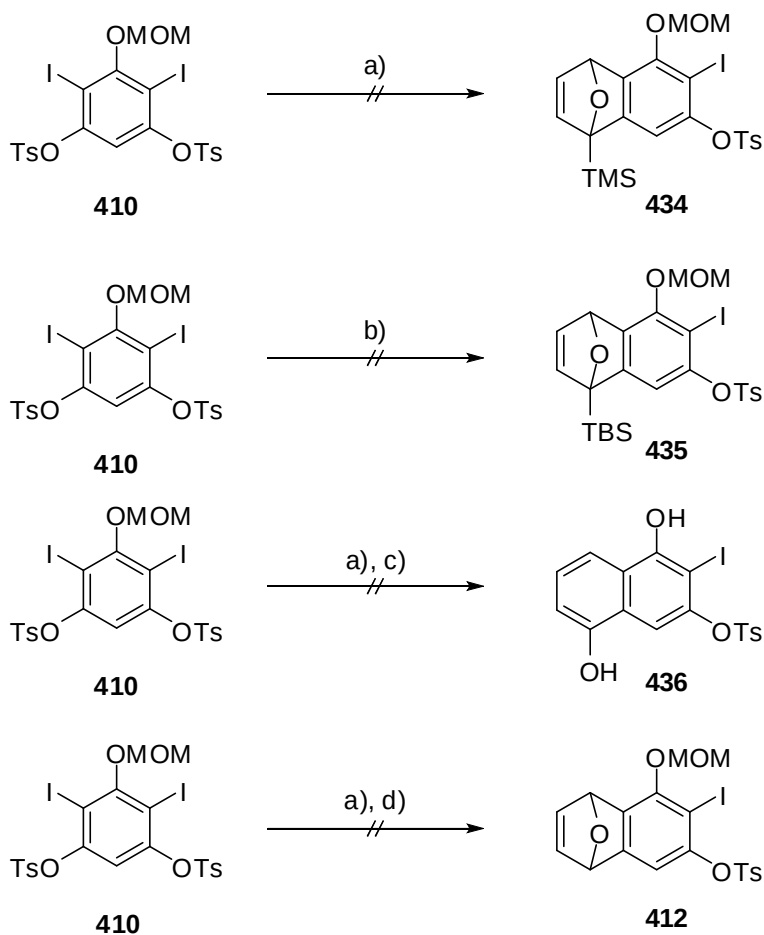
Another type of furan was then investigated, where the substituents causing asymmetry were closer to the centre of reactivity. Accordingly, the use of 2-silyl substituted furans in order to induce regioselectivity was explored. To this end, the simple 2-TMS and 2-TBS furans were made *via* lithiation and quenching (Scheme 140). The trimethylsilyl furan **432** is less sterically demanding, but it should be uncomplicated to remove the silyl group, whereas the *tert*-butyldimethylsilyl furan **433** would be envisaged to provide more of a strongly unsymmetrical reaction intermediate, but would be more challenging to remove. These were used as model furans for the Diels-Alder reaction.



Reagents and conditions: a) i) *n*-BuLi, THF, 0 °C, ii) TMS-Cl, 23 °C, 72%; b) i) *n*-BuLi, THF, 0 °C, ii) TBS-Cl, 23 °C, 69%

Scheme 140: The Synthesis of Furans **432** and **433**

Various procedures were explored in order to discover if the aryne-furan reaction between **410** and **432** or **433** was regioselective. Firstly, the reaction with furan **432** was examined in order to obtain cycloadduct **434**, and although there was spectroscopic evidence of the desired product, it was relatively impure and a mixture of regioisomers. The same reaction with the bulkier furan **433** was attempted, but this reaction yielded a complex mixture of intractable products. Attempts to aromatise or desilylate the product in a one-pot or on an unpurified initial product were unsuccessful, with similarly complex mixtures (Scheme 141).



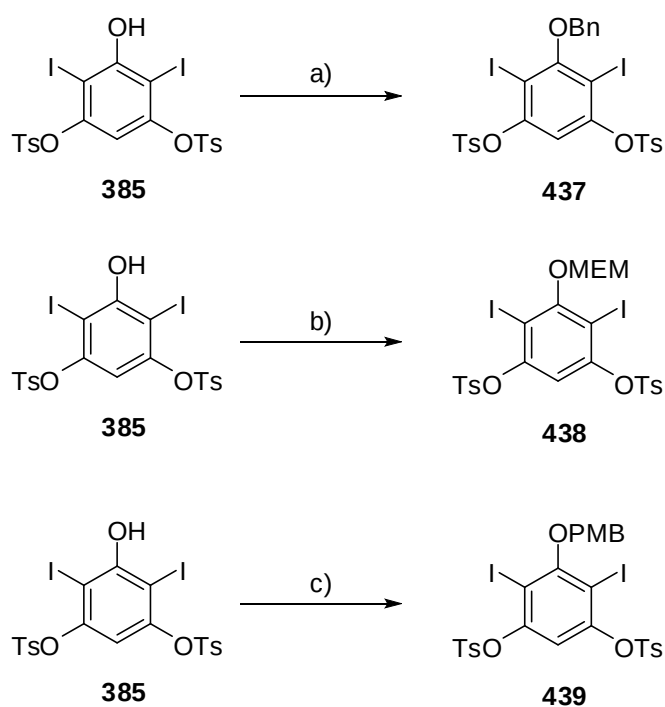
Reagents and conditions: a) i) *i*-PrMgCl, , THF, $-78\text{ }^{\circ}\text{C}$, ii) **432**, $-78\text{ }^{\circ}\text{C}$ to rt; b) i) *i*-PrMgCl, THF, $-78\text{ }^{\circ}\text{C}$, ii) **433**, $-78\text{ }^{\circ}\text{C}$ to rt; c) MsOH, MeOH; d) TBAF, THF, $0\text{ }^{\circ}\text{C}$

Scheme 141: The Reactions of Silylated Furans with the Aryne Derived from Precursor **410**

In all cases, no satisfactory results were obtained from any of these experiments, and so this type of disconnection was deemed to be not useful for the synthesis of the target molecule due to its low yield and lack of regioselectivity and so attention was turned back to a route forming the key carbon-carbon bond by C-aryl glycosidation. It was felt that the MOM group was proving to be too labile for the conditions required for the glycosidation, and was not only preventing the desired transformation from occurring but undergoing deprotection at the MOM ether centre.

Attention was therefore turned to a different protecting group, one that would be robust enough to survive the necessary steps but be selectively removed when

required. Silicon-based groups were earlier demonstrated to not withstand the aryne-generating conditions employed, so the methoxyethoxymethyl (MEM), benzyl and *para*-methoxybenzyl (PMB) groups were examined. Diiodophenol **385** was successfully protected as benzyl ether **437**, MEM ether **438** and PMB ether **439** using standard conditions (Scheme 142). The lability of these groups to the Lewis acid systems used in the C-glycosidation was examined, and the benzyl and PMB ethers were stable, but the MEM ether decomposed, albeit slower than the MOM ether. Therefore, the benzyl ether was chosen, due to its stability and orthogonal deprotection methods, though it is worth noting that the PMB ether should be able to be used in all following cases in lieu of the benzyl ether if required.

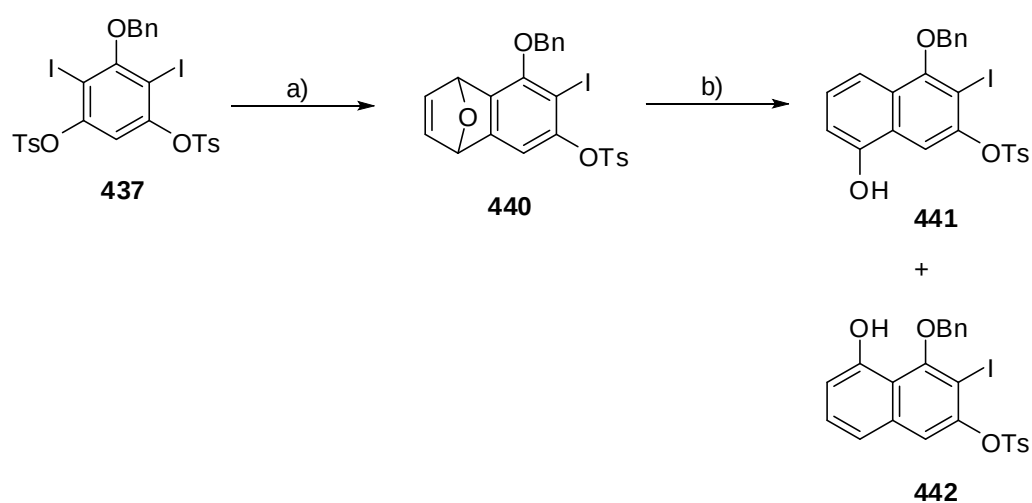


Reagents and conditions: a) Cs_2CO_3 , BnBr, THF, 91%; b) MEM-Cl, $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 , 82%; c) Cs_2CO_3 , TBAI, PMB-Cl, THF, Δ , 74%

Scheme 142: The Synthesis of Alternative Aryne Precursors **437**, **438** and **439**

Benzyl ether **437** was subjected to the conditions of the cycloaddition developed previously, and was successfully converted into the corresponding aryne, undergoing the desired reaction with furan to give cycloadduct **440** in 61% yield, slightly increased from the corresponding reaction when the analogous MOM ether was used. Although it was envisaged that the benzyl-protected cycloadduct should be able to be aromatised with acid, it was found that trifluoroacetic acid had no effect and that

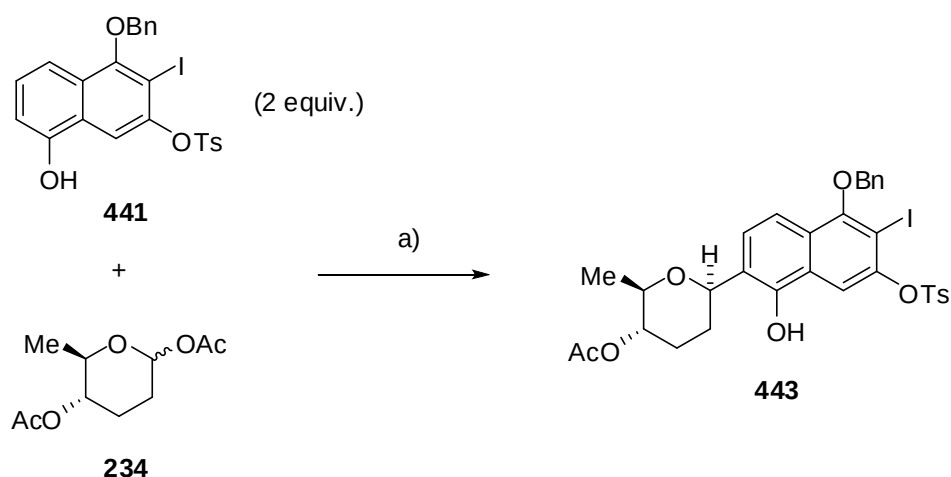
para-toluenesulfonic acid or methanesulfonic acid gave the aromatised product, naphthol **441**, but with impurities. Copper (II) triflate has been used to aromatise cycloadducts¹⁶⁷ and although this worked well on smaller scale (< 0.5 mmol), on larger scale the reaction suffered from numerous side-products and was not easily purifiable. Therefore, naphthol **441** was obtained using the previous trimethylsilyl trifluoromethanesulfonate-mediated conditions. Unfortunately, as with the MOM-ether, the formation of the initial silyl ethers is not regioselective and so an approximately 1:1 mixture of separable naphthols **441** and **442** was formed (Scheme 143).



Reagents and conditions: a) i) *i*-PrMgCl, THF, $-78\text{ }^{\circ}\text{C}$, ii) furan, $-78\text{ }^{\circ}\text{C}$ to rt, 61%; b) i) TMS-OTf, 2,6-lutidine, CH_2Cl_2 , ii) TBAF, THF, 55%.

Scheme 143: The Synthesis of Benzyl-Protected Naphthols **441** and **442**

Naphthol **441** was then used as the glycosyl acceptor in the *C*-glycosidation (Scheme 144). A similar range of Lewis acids were considered for the glycosidation and the experiments and results are detailed in Table 17. In all cases, it was noted that naphthol **441** was recoverable from the reaction mixture and, in contrast to the MOM analogue, did not decompose under the reaction conditions.



Reagents and conditions: See Table 17

Scheme 144: The Synthesis of C-Aryl Glycoside **443**

Entry	Lewis Acid	Additive	Solvent	Temperature (°C)	Result
1	Cp ₂ HfCl ₂	AgClO ₄ , 4Å MS	CH ₂ Cl ₂	−78 to 23	443 , 58%
2	BF ₃ ·OEt ₂	4Å MS	CH ₂ Cl ₂	−78 to 23	Complex mixture
3	Sc(OTf) ₃	Drierite	DCE	−40 to 23	443 , 47%
4	TMS-OTf	-	MeCN	0 to 23	443 and other products
5	TMS-OTf	AgClO ₄	MeCN	0 to 23	443 and other products

Table 17: Reaction Conditions Examined for C-Aryl Glycosidation of Naphthol **441**

Assessing the outcome of these experiments is more complicated than in most cases, for a couple of reasons. Firstly, the C-glycoside was formed, but in many different experiments a second species, probably the O-glycoside, was observable by TLC analysis and in the ¹H NMR spectrum of the crude product. This species has a very similar R_f value to the C-glycoside, and both species are of a similar value to the naphthol, which is always present in excess, so will always be present in the crude reaction mixture. This makes separation relatively difficult. However, in some cases,

the formation of this second product was negligible, and this allowed isolation and characterisation of the *C*-glycoside, confirming its identity using NMR and mass spectrometry.

With this knowledge, the reaction could be seen to be most successful with the scandium triflate and hafnocene dichloride/silver perchlorate systems. Both gave the *C*-glycoside **443** in synthetically useful amounts, and with extensive chromatographic optimisation, reasonable yields of pure product were obtainable. With the hafnocene dichloride/silver perchlorate system, **443** was synthesised in a yield of 58% and with the scandium triflate system, 47%.

However, it is a frustrating aspect of this reaction that these yields were not always reproducible, as on different occasions the *C*-aryl glycoside **443** was not the major product and sometimes a significant amount of a second product was observed, the identity of which was speculated as either *O*-glycoside **444** or *para*-*C*-glycoside **444a**.

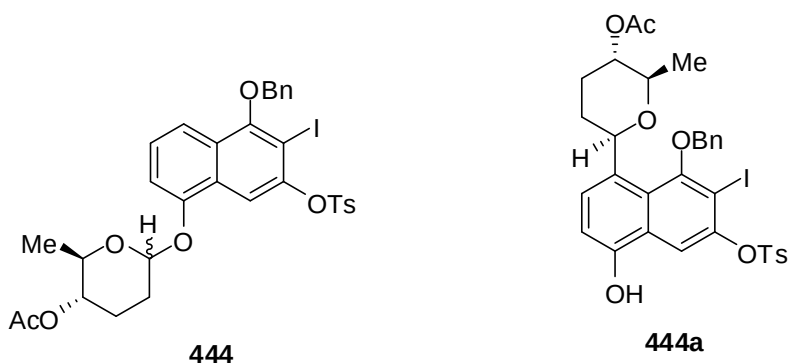


Figure 10: Potential Side Products *O*-Glycoside **444** and *C*-Glycoside **444a**

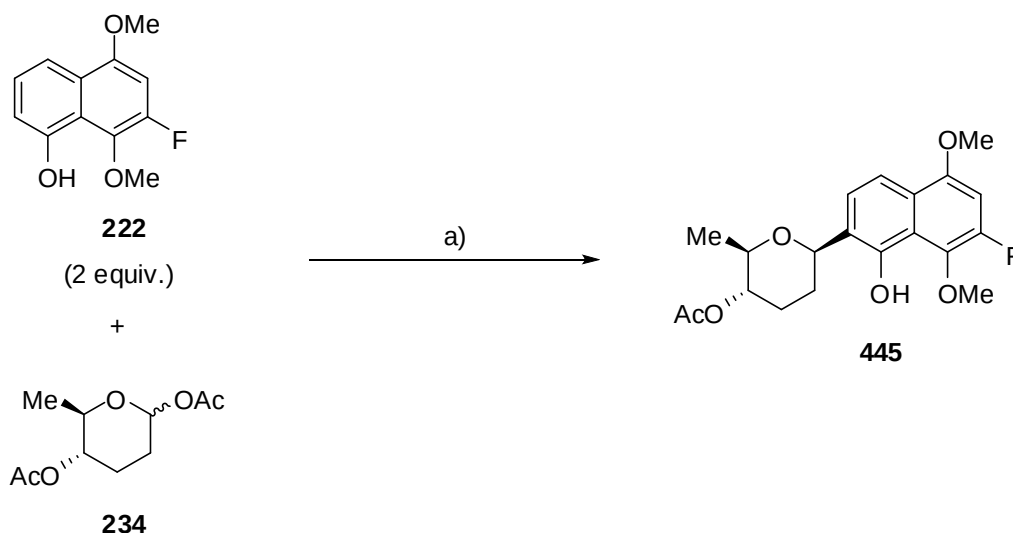
This second product has a similar R_f to *C*-aryl glycoside **443** and on occasion has been the major product of the reaction. ^1H NMR shows that it still has the *ortho*-proton that is substituted in **443**, and mass spectrometry data indicates that the species has the same mass as *C*-aryl glycoside **443**, indicating it is an isomer. All the glycosidic resonances are present at the same integrals, confirming that the sugar unit has attached to the naphthol and the singlet resonance which corresponds to the proton *ortho* to the tosylate group is shifted downfield with respect to *ortho*-glycoside **443**.

A point in favour of the *O*-glycoside is that it is demonstrated in the previous work of Suzuki that the reaction proceeds through the *O*-glycoside as an intermediate, and so therefore it can be speculated that the rearrangement step is particularly slow on the substrate examined here.

However, were this species to be *O*-glycoside **444**, some further conversion of the product obtained into the desired *C*-glycoside **443** should be possible by re-submitting the species to the reaction conditions employed to drive the reaction to the irreversible *C*-glycosidation even if it doesn't convert fully. However, even with prolonged reaction times, subjecting the species obtained from the initial reaction to the hafnocene dichloride or scandium triflate conditions resulted in absolutely no conversion and only starting material was recovered. This would suggest that this species is not the *O*-glycoside **443** and the *para*-*C*-glycoside **444a** is a more likely candidate for the identity of this species.

After experimental work was concluded, further investigations in the group later discovered conditions which enabled this side product to consistently be the main product of the reaction and therefore isolated pure. Detailed HMBC NMR studies determined that the product of the reaction was in fact *para*-*C*-glycoside **444a**, despite there being very little precedent for the *para*-isomer being observed in the literature.

The reason for the inconsistency of reaction remains unclear. Due to the fact that the reaction worked on two separate occasions cleanly with a different naphthol **222** in a test reaction, giving only *C*-glycoside **445** as the major product (Scheme 145), it is most likely that the issue with the reaction is with the naphthol component.



Reagents and conditions: Cp_2HfCl_2 , AgClO_4 , 4Å MS, CH_2Cl_2 , -78°C to rt, 61%

Scheme 145: The Synthesis of C-Aryl Glycoside **445**

Naphthol **222**, along with the vast majority of naphthols used in the literature precedent, are relatively electron-rich compared to naphthol **441** that is required for the synthesis, as the methoxy substituents in naphthol **222** reinforce each other in the directing of electron density, unlike those of naphthol **441**. The formation of the *O*-glycoside will not be significantly affected by this, but the Friedel-Crafts-type *C*-glycosidation step will be faster the more electron-rich the aromatic system is. Presumably this has an effect on the regioselectivity, and it would suggest that the *ortho*-product is favoured with the more electron-rich systems, whereas when slower, more electron-poor naphthols are used, both *ortho*- and *para*-isomers are obtained.

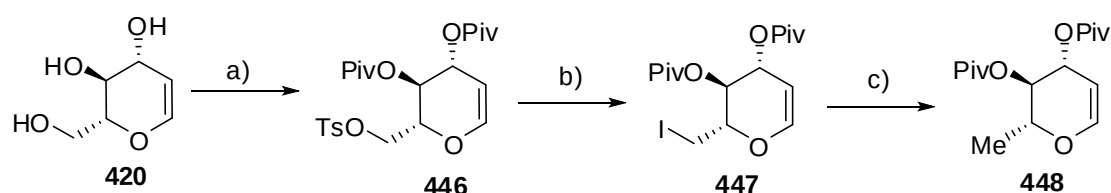
The difference in regioselectivity can only be ascribed to electronic effects as the steric environments of the *ortho*-positions vs the *para*-positions of naphthols **222** and **441** are very similar, and in fact the benzyl ether, as opposed to the methyl ether, present in the position *peri* to the *para*-position in naphthol **440** suggests that *para*-substitution would be more difficult on steric grounds, not less, and that substitution in the *para*-position is despite steric arguments, not because of them.

As well as the inherent electronic nature of the naphthol, the other concern is the purity of the naphthol and whether different levels of impurity in the batches of naphthol synthesised was having a prohibitive effect on the *C*-glycosidation step. Although by NMR spectroscopy and TLC analysis the samples of naphthol **441** are

pure after chromatography, the solid obtained is often discoloured. Although no significant impurity can be detected, but it is possible that the C-glycosidation is affected by trace amounts of these unknown impurities, but all efforts to further purify the naphthol have not resulted in notable improvements.

While the inherent nature of the glycosidation reaction was being probed, another problem remaining was the similarity in R_f of the glycosides to the naphthol. Therefore, the use of a less polar glycoside was investigated, in order to make separation of the glycosides from the naphthol easier. Additionally, the acetate protecting group on the glycoside would also not be appropriate for later steps, so replacing it with another group would be advantageous. Given these factors, the pivalate group was examined as an alternative.

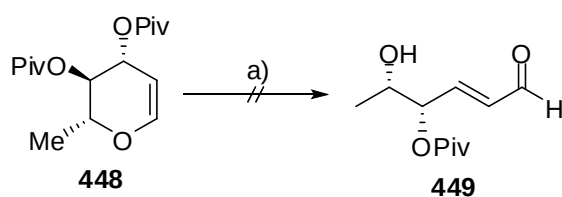
It was envisaged that similar methodology could be used in order to synthesise the pivalate analogue, and so the dipivalate-protected rhamnal **448** was synthesised in a similar manner to the acetate analogue, described previously (Scheme 146).



Reagents and conditions: a) i) TsCl, C_5H_5N , ii) PivCl, 76%; e) NaI, *i*-BuCOMe, Δ , 88%; f) $(SiMe_3)_3SiH$, ABCN, PhMe, Δ , 86% or Bu_3SnH , ABCN, PhMe, Δ , 89%

Scheme 146: Synthesis of Pivalate-Protected Rhamnal **448**

The next stage would be the thermally-induced Ferrier-type rearrangement to give aldehyde **449** (Scheme 147). However, when dipivalate **448** was subjected to the same conditions as for the diacetate as described previously, no reaction occurred and only starting material was recovered. Heating for longer, or with acetic acid as a catalyst resulted in similar outcomes. When **448** was heated with hafnium tetrachloride and zinc diiodide¹⁶⁸ no product was recovered, presumably because under the conditions employed the sugar was globally deprotected and was water-soluble.

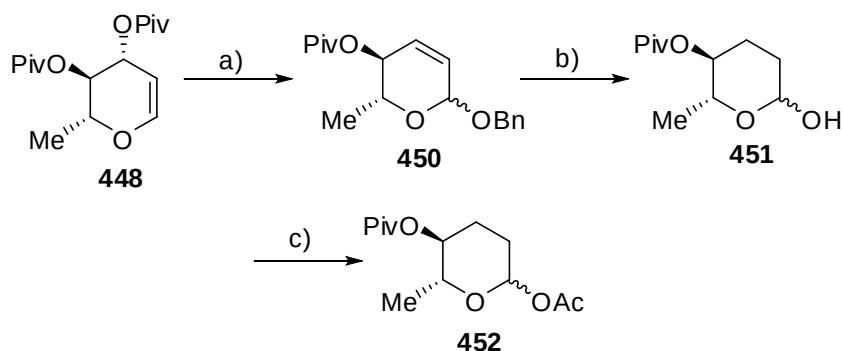


Reagents and conditions: a) H₂O, 80 °C or H₂O, AcOH, 80 °C or HfCl₄, ZnI₂, MeCN, Δ.

Scheme 147: Attempted Conversion of Rhamnal **448** into Aldehyde **449**

With this methodology seemingly inapplicable to the pivalate sugar, an alternative route was examined, whereby a Ferrier rearrangement was utilised as before, but Lewis acid catalysed, with benzyl alcohol as the nucleophilic species. It is advantageous to use this as it can be removed under the same conditions required to hydrogenate the alkene, revealing lactol **451** which can be acetylated.

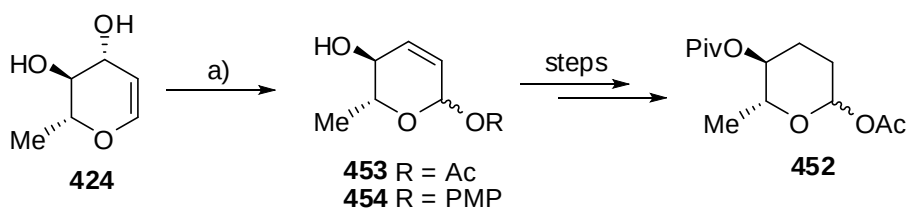
Accordingly, **448** was treated with various Lewis acids in order to obtain the Ferrier product **450**. Boron trifluoride diethyl etherate and tin tetrachloride were examined but gave somewhat complicated mixtures of products. Scandium triflate gave better results, in that the desired product was the major component, but even after chromatography could not be isolated completely pure. The impure benzyl ether **450** was then converted into lactol **451** with palladium hydroxide on charcoal, as palladium on carbon alone failed to remove the benzyl ether. Lactol **451** was then acetylated (Scheme 148), but many of the impurities from the Ferrier rearrangement remained inseparable from the product and so a cleaner route to acetate **452** was needed.



Reagents and conditions: a) $\text{Sc}(\text{OTf})_3$, BnOH , CH_2Cl_2 , 56-72% (impure); b) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, EtOAc , EtOH , 65% (impure) c) Ac_2O , $\text{C}_5\text{H}_5\text{N}$, CH_2Cl_2 , 84% (impure)

Scheme 148: Conversion of Rhamnal **448** into Glycosyl Acetate **452**

It has been demonstrated¹⁶⁹ that Mitsunobu reactions on the glycal motif is $\text{S}_{\text{N}}2'$ selective so that if standard Mitsunobu conditions are applied to **424**, an acetal of the type **453** is expected rather than direct displacement. If acetic acid is used ($\text{R} = \text{Ac}$), the desired acetate functionality would be introduced efficiently. Otherwise, the use of *para*-methoxyphenol ($\text{R} = p\text{-OMeC}_6\text{H}_4$) will be examined as the resulting *para*-methoxyphenyl (PMP) group can be removed under oxidative conditions,¹⁷⁰ and the resulting lactol can be acetylated to provide the desired glycosyl acetate **452** (Scheme 149).

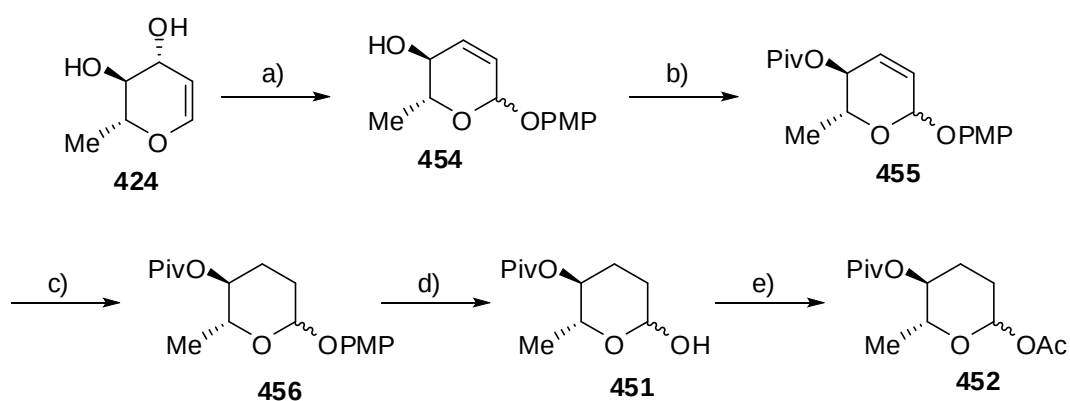


Reagents and conditions: a) PPh_3 , DIAD, R-OH , CH_2Cl_2

Scheme 149: Alternative Route to Acetate **452** via a $\text{S}_{\text{N}}2'$ -Mitsunobu Reaction

When rhamnal **424** was subjected to standard Mitsunobu conditions with acetic acid, the desired product was only formed in very low yields. The species identified as the product co-eluted with the hydrazide resulting from reduction of DIAD and so it was difficult to assess the yield accurately, but it was certainly under 10%. When *para*-methoxyphenol was used as the nucleophile, the desired product **454** was obtained in higher yields. Originally, the azodicarboxylate used was DIAD, but it was found that,

as before, its by-product co-eluted with the desired product in all solvent systems, and so di-*tert*-butylazodicarboxylate (DTAD) was instead used. The hydrazine resulting from reduction of DTAD also co-eluted but to a lesser extent and gave a cleaner product, albeit still impure. After pivaloyl protection of the mixture, pivalate **455** was obtained and could be fully purified. The pivalate was thus obtained in 48% yield over the two steps. The remaining steps were facile transformations, *viz.* hydrogenation to give **456** in 82% yield, oxidative deprotection of the PMP group with CAN to give lactol **451** in 84% yield and acetylation of the anomeric hydroxyl group in 76% yield. This sequence cleanly gave the desired glycosyl acetate **452** (Scheme 150).

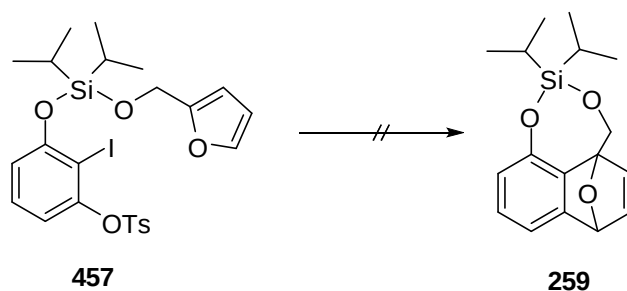


Reagents and conditions: a) PPh_3 , DTAD, *p*-OMeC₆H₄OH, CH₂Cl₂, 0 °C to rt; b) C₅H₅N, PivCl, DMAP, CH₂Cl₂, 48% (over 2 steps); c) H₂, Pd/C, EtOH, 82%; c) aq. CAN, MeCN, 84%; d) Ac₂O, C₅H₅N, CH₂Cl₂, 76%.

Scheme 150: Conversion of Rhamnal **424** into Acetate **452**

6.5 Refinement of the Aryne Precursor and Examination of C-Glycosidation Conditions

At this time, it became apparent, due to model studies conducted elsewhere within the group, that the use of an iodotosylate as an aryne precursor for the intramolecular aryne-furan Diels-Alder reaction with a silaketal linker was not appropriate. Under all types of condition examined, the desired cycloadduct was not obtained (Scheme 151), so it was known that the iodonitrile analogue was required for the synthesis of the target molecule.¹⁷¹



Scheme 151: Attempted Conversion of Iodotosylate **457** into Cycloadduct **259**

The tosylate functionality can be converted to the triflate before the silaketal is formed, but given that the synthetic strategy requires the presence of the glycosidic moiety at this stage in the synthesis, it was felt that the hydrolysis of the tosylate would be excessively harsh conditions to impose this late in the synthesis. The synthesis of the equivalent tris(triflate) **458** was explored, but its lack of appearance in the literature is explained by the failure of the reaction between phloroglucinol and a range of triflating agents: triflic anhydride, *N*-phenylbis(trifluoromethanesulfonimide) or *p*-nitrophenyl triflate (Scheme 152). Therefore investigation into **458** was discontinued.

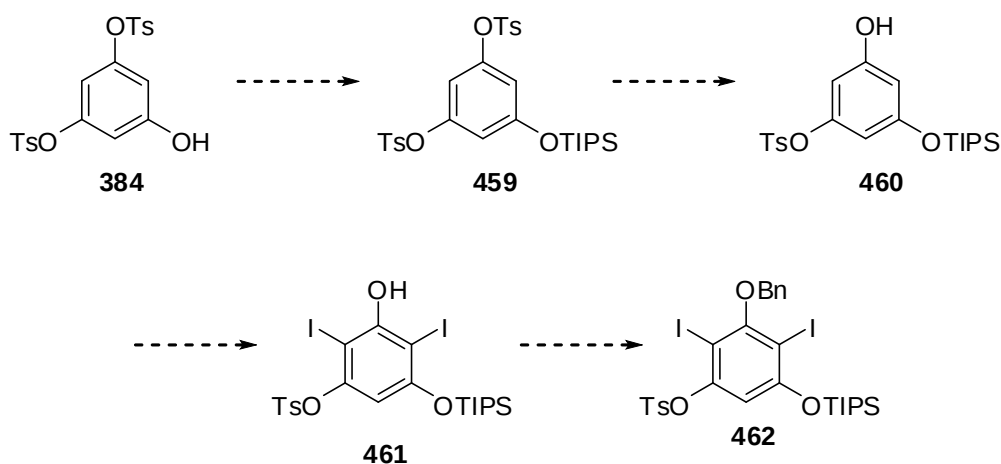
Reagents and conditions: a) TiF_2O , *i*- Pr_2NEt , CH_2Cl_2 , -78°C to rt or PhNTf_2 , *i*- Pr_2NEt , CH_2Cl_2 or 4- $\text{O}_2\text{NC}_6\text{H}_4\text{OTf}$, K_2CO_3 , DMF

Scheme 152: Attempted Triflation of Phloroglucinol

Even if it were to be synthesised, it would be inappropriate to have the bis(triflate) functionality present before the cycloaddition step, as a controlled single cycloaddition would be unfeasible with this substrate. One of the triflate groups would need to be hydrolysed and converted to something less prone to elimination to form an aryne.

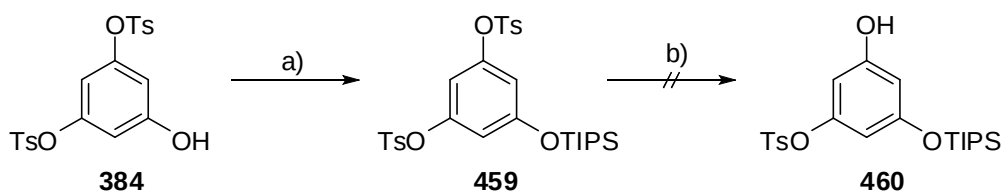
Therefore, an intermediate protecting group is required, one which will not be a sufficiently good leaving group that it will undergo a cycloaddition under the established aryne-generating conditions but can be removed under milder conditions than those required for the hydrolysis of a tosylate.

With these criteria in mind, the use of the TIPS group was explored. It is able to be removed with fluoride sources and it is known from earlier work in Section 5.5 that it is stable to arynes and aryne-generating conditions. The original route was modified to introduce the silyl ether at an early stage, and hydrolyse the tosylate, iodinate and benzylate as before in order to obtain benzyl ether **462** (Scheme 153).



Scheme 153: Proposed Route to Benzyl Ether **462**

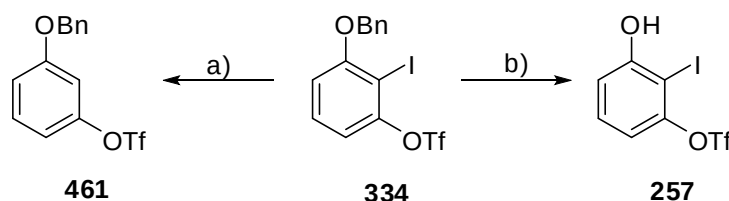
Phenol **384** was protected as the TIPS ether under standard conditions in 86% yield. However, when silyl ether **459** was subjected to the standard hydrolysis conditions, it was found that the silicon centre was far more reactive and that only desilylation occurred giving back phenol **384** (Scheme 154). Weaker bases had no effect and only starting material was recovered.



Reagents and conditions: a) imidazole, DMAP, TIPS-Cl, CH₂Cl₂, 86%; b) KOH, H₂O, MeOH.

Scheme 154: Attempted Synthesis of Phenol **460**

Instead, two other routes were examined. Firstly, a route involving the synthesis of the deiodinated analogue was proposed, as the presence of the iodine atom has been shown to affect the debenzylation step in model studies. It was shown that under normal hydrogenation conditions, benzyl ether **461** is the exclusive product, from deiodination. However, under acidic conditions, the iodide **251** is the major product, the desired chemoselectivity for the synthesis (Scheme 155).

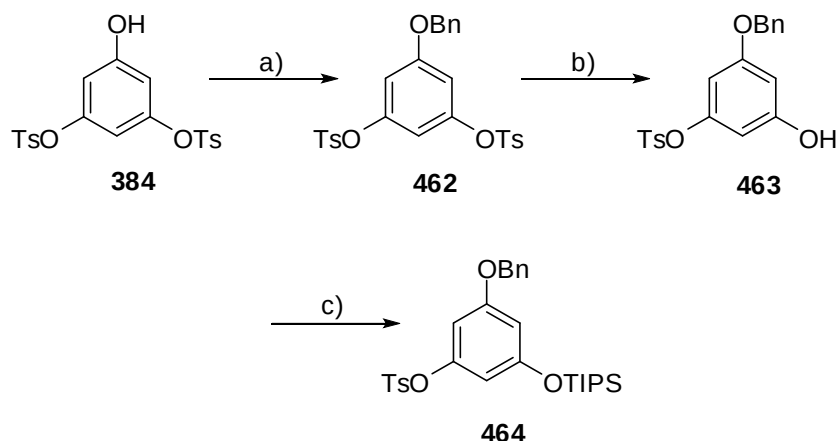


Reagents and conditions: a) H₂, Pd/C, EtOH, 84% (crude); b) H₂, Pd/C, aq. HCl, EtOAc, 76% (crude).

Scheme 155: Reactivity of **334** with Palladium on Carbon

Although these conditions should prove to debenzylate in the real system effectively, the possibility of the acidic conditions being incompatible with other functionalities remains. Therefore, synthesis of a substrate where the iodide is not present and could be added after the debenzylation would be a desirable alternative. With this in mind, a synthesis was considered in which the sequence proceeded as before except the iodination step only delivers a single iodine functionality to the substrate and thus, after the aryne generation, there are no halide functionalities to interfere with the debenzylation.

Accordingly, the silyl ether **464** was synthesised in three steps from phenol **384**, using standard methodology: benzylation to give benzyl ether **462** in 86% yield, hydrolysis to phenol **463** in 70% yield and silylation to give silyl ether **464** in 85% yield (Scheme 156).

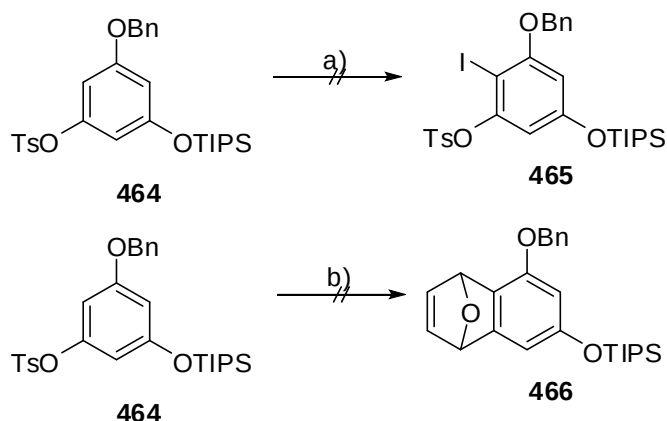


Reagents and conditions: a) Cs_2CO_3 , BnBr, THF, 86%; b) KOH, H_2O , MeOH, dioxane, 70%; c) imidazole, DMAP, TIPS-Cl, CH_2Cl_2 , 85%.

Scheme 156: The Synthesis of Silyl Ether **464**

With this substrate in hand, the selective mono-iodination was examined. If **464** is treated with an alkyllithium, the TIPS group will direct lithiation away from *ortho*-positions on steric grounds and given the substitution pattern on the aromatic ring, lithiation can only occur between the benzyl ether and the tosylate functionalities. If the intermediate organolithium species were stable, it could be quenched with iodine and then the cycloaddition can be conducted with the more controlled, higher-yielding conditions using *iso*-propylmagnesium chloride. Alternatively, the lithiated species may be unstable and collapse to the equivalent aryne even at low temperature. If it is generated in the presence of furan, cycloadduct **466** would be obtained.

However, despite all attempts to lithiate **464**, the substrate resisted reaction at $-78\text{ }^\circ\text{C}$, even with *tert*-butyllithium. Even on warming, no iodide **465** was formed. Similarly, when warmed in the presence of furan, no cycloadduct **466** was detected, only partial recovery of starting material (Scheme 157). It is clear that if any reaction is occurring, it is not in the desired manner and so the lithiation route was abandoned.



Reagents and conditions: a) i) *n*-BuLi, THF, $-78\text{ }^{\circ}\text{C}$ or *t*-BuLi, TMEDA, THF, $-78\text{ }^{\circ}\text{C}$, ii) I_2 , $-78\text{ }^{\circ}\text{C}$ to rt; b) *n*-BuLi, THF, furan, $-78\text{ }^{\circ}\text{C}$ to rt or *t*-BuLi, TMEDA, furan, THF, $-78\text{ }^{\circ}\text{C}$ to rt

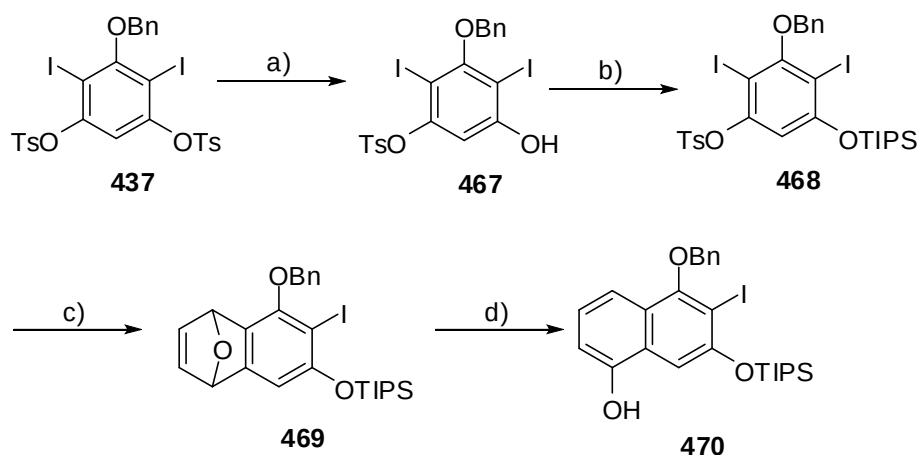
Scheme 157: Attempted Functionalisation of Tosylates **464**

Meanwhile, attention was turned back to the double iodide analogue, as the singly-iodinated product was proving elusive. Benzyl ether **437** was therefore hydrolysed and TIPS protection of the revealed phenol gave silyl ether **468**. This substrate should only generate an aryne at one site, i.e. the iodotosylate, as the $-\text{OTIPS}$ functionality directs metallation away from itself, due to steric constraints. Furthermore, even were it to metallate, the $-\text{OTIPS}$ moiety is not a sufficiently good leaving group to induce aryne formation, and as it is expected that intermolecular magnesium-iodine can readily occur and so, with only one equivalent of Grignard reagent present, metallation is effectively reversible. Therefore, upon warming, irreversible elimination of a magnesium tosylate species from the *ortho*-magnesium tosylate would drive the equilibrium towards magnesiation at the desired position. These two factors mean that the treatment of iodotosylate **468** with one equivalent of Grignard should result in no deiodination in the position *ortho* to the silyl ether and still form the aryne as before.

When iodotosylate **468** was subjected to standard aryne-generating conditions in the presence of furan, cycloadduct **469** was isolated in 85% yield (Scheme 157). This result was a far higher yield than previous cycloadditions on the double aryne precursors, e.g. the double tosylate analogue only yielding the cycloadduct in 61% yield. This indicates that the fundamental reactivity of this system is very high and presumably the multiple possible sites of reaction were the main restriction on the yield previously. Even though extra steps are required in synthesising the silyl ether

aryne precursor **468**, the enhanced yield of the key cycloaddition step, repeatable from 0.5 mmol to 50 mmol, vindicates this robust and reproducible route as being of comparable overall yield.

Furthermore, it was found that cycloadduct **469** could be aromatised with Brønsted acids. Trifluoroacetic acid gave little conversion even after extended reaction times, but *para*-toluenesulfonic acid was found to be suitable and generate naphthol **470** in 74% yield, though this reaction is unoptimised and it is envisaged that higher yields are achievable with further investigation into optimal conditions (Scheme 158).

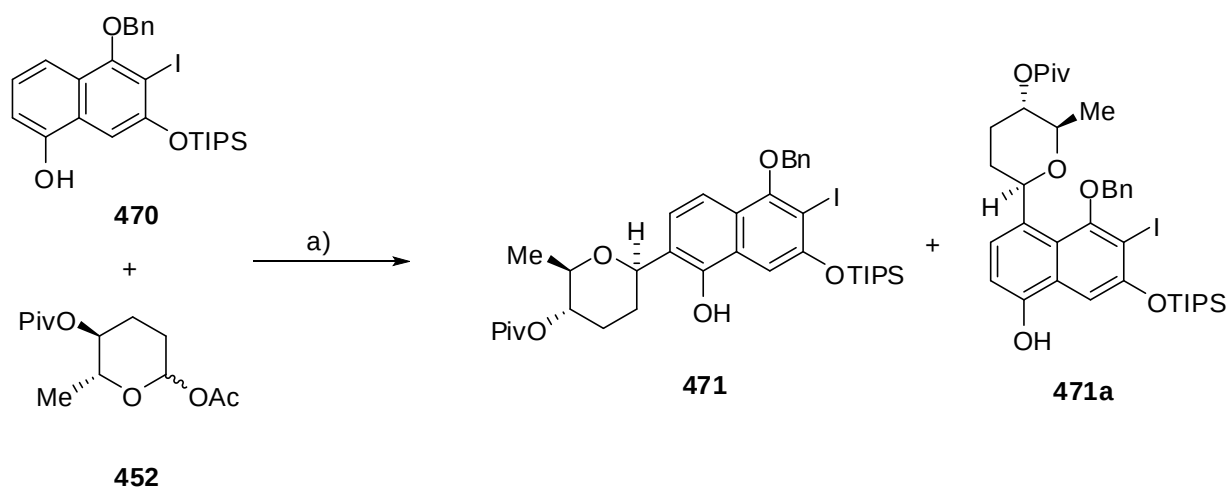


Reagents and conditions: a) KOH, H₂O, MeOH, dioxane, 81%; b) imidazole, DMAP, TIPS-Cl, CH₂Cl₂, 87%; c) i) *i*-PrMgCl, THF, -78 °C, ii) furan, -78 °C to rt, 85%; d) TsOH, CH₂Cl₂, 74%

Scheme 158: Synthesis of Naphthol **470** from Tosylate **437**

At this juncture, there was insufficient time to investigate the *C*-aryl glycosidation of naphthol **470** other than a test reaction in which naphthol **470** and acetate **452** were subjected to hafnocene dichloride in the presence of silver perchlorate, conditions used previously in the successful synthesis of *C*-aryl glycosides. In this reaction, two new species of a very similar *R_f* value to each other were present, by TLC analysis. These products were not separable from each other, but the NMR spectra of this mixture of products is consistent with one species being the desired *C*-aryl glycoside **471** and the other species being a similar side-product as before, assigned as the *para*-*C*-glycoside **471a**, though lack of material and time precluded proper characterisation. This preliminary result indicates that change of identity of the naphthol to the TIPS-protected analogue has not had any positive or negative effect on the progression of

the glycosidation and that this reaction must be optimised in order to make it reproducibly yield the *ortho*-C-glycoside **471** (Scheme 159).



Reagents and conditions: a) Cp_2HfCl_2 , AgClO_4 , 4Å MS, CH_2Cl_2 , -78°C to rt

Scheme 159: Attempted C-Aryl Glycosidation with Naphthol **470** to Obtain **471**

Chapter 7: Conclusion and Further Work towards the Total Synthesis of Sch 47554

7.1: Conclusion

Studies were conducted on model systems relevant to the synthesis of the aromatic core of Sch 47554 and Sch 47555. Previous studies in the group had shown that the use of methyl-protected heavily oxygenated aromatic systems were useful in their ease to synthesise and good acceptors in glycosidation reactions, enabling the synthesis of the glycosidic portion of the western half of *ent*-Sch 47554.

However it was found in the current studies that the type of aromatic systems used previously are impractical for further elaboration of the molecule. Deprotection of these substrates is often impractical due to the harsh conditions required, and that when deprotection was viable, many systems were prone to oxidation and other uncontrolled side reactions. As a result, using these types of aromatic system, synthesis of stable aryne precursors that are able to be attached *via* a silaketal linker to the furan required for the key intramolecular aryne-furan cycloaddition proved elusive.

Therefore, a less-oxygenated aromatic system was investigated, and after extensive experimentation, naphthols **441** and **470** were successfully synthesised. The less oxygenated systems proved more stable to deprotection reactions thus far, but as they are less electron-rich, have proven to be less potent glycosyl acceptors in the key *C*-aryl glycoside formation. Nevertheless, *C*-glycosidation has proven possible on these substrates, with the synthesis of **443**. It is noted that at present the reaction is somewhat capricious, as formation of a major side-product, putatively assigned as the corresponding *O*-glycoside has sometimes complicated the reaction. Further optimisation of the glycosidation reaction therefore remains to be carried out.

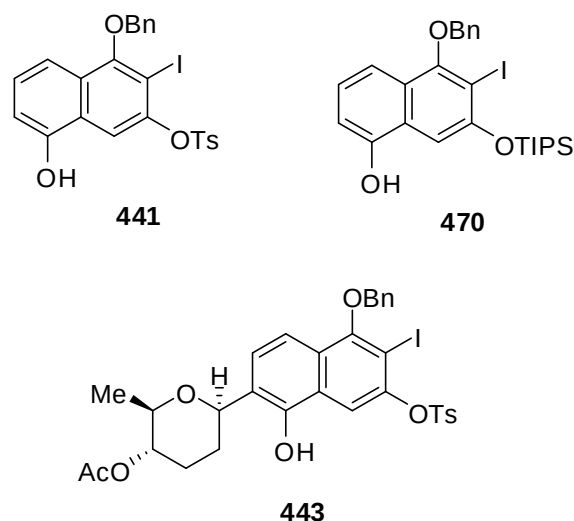


Figure 11: Naphthols **441** and **470** and C-Aryl Glycoside **443**

It was also discovered that the acetate-protected sugar unit was unsuitable for use in the glycoside reaction, due to the difficulties in separating it from the naphthol. Therefore a route to the pivalate-protected sugar unit was developed, and this sugar is far more easily separable from the naphthol, though with the sensitivity of the C-glycosidation this has not been fully exploited yet.

In conclusion, these studies have significantly advanced the synthesis of Sch 47554 and Sch 47555. Many of the model studies were ultimately unsuccessful, but important results were gained from these experiments, in determining the type of fragment that can be used as intermediates in the total synthesis and when attention was turned to the real system this was demonstrated, as progress was more forthcoming. Although the target molecules are still a little further away from being completed, robust methodology for the individual aromatic and glycosidic fragments has been established. The synthesis of the furan fragment and investigations into the intramolecular Diels-Alder with a model aryne have also been undertaken in the group (*vide infra*), meaning that all the key carbon-carbon bonds have been made in fragments or model studies. This groundwork means that the total synthesis of Sch 47554 and Sch 47555 is considerably nearer and once all the work presented is completely optimised and used together, the synthesis will be in an advanced state and it is believed that from this platform, with further experimentation, the total synthesis of the target molecules will be successful.

7.2 Other Work Towards the Total Synthesis of Sch 47554 and Sch 47555

Concurrent to the work presented here, other aspects of the synthesis of Sch 47554 and Sch 47555 have been investigated elsewhere in the group. The synthesis of furan **210** required as a key intermediate in the synthesis of the target molecules was investigated and after extensive research a route to a suitable furan was achieved.^{171,172} Investigations into the intramolecular Diels-Alder reaction were also undertaken using the actual furan moiety that it is envisaged will be used in the synthesis of the target molecules.¹⁷¹ These results will be briefly described in this section.

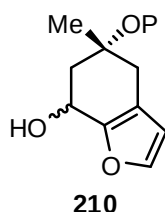
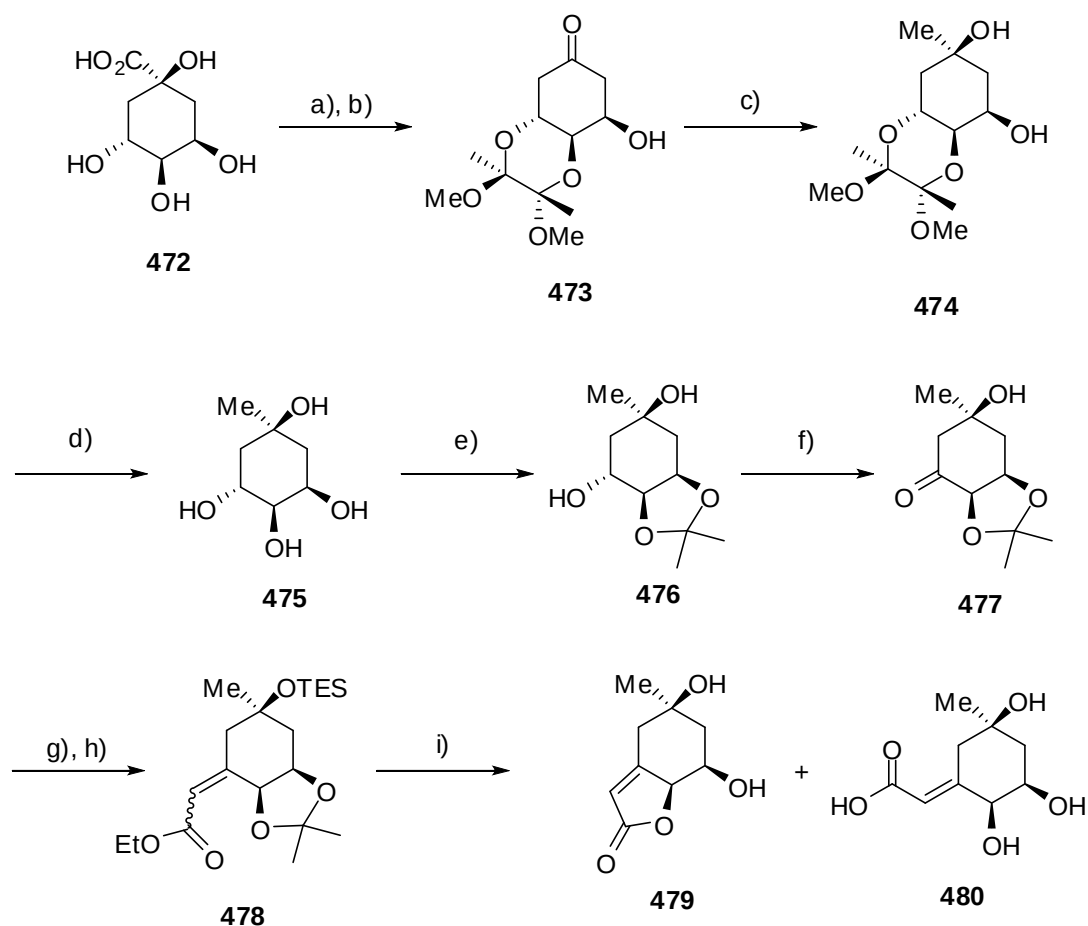


Figure 12: Furan **210**

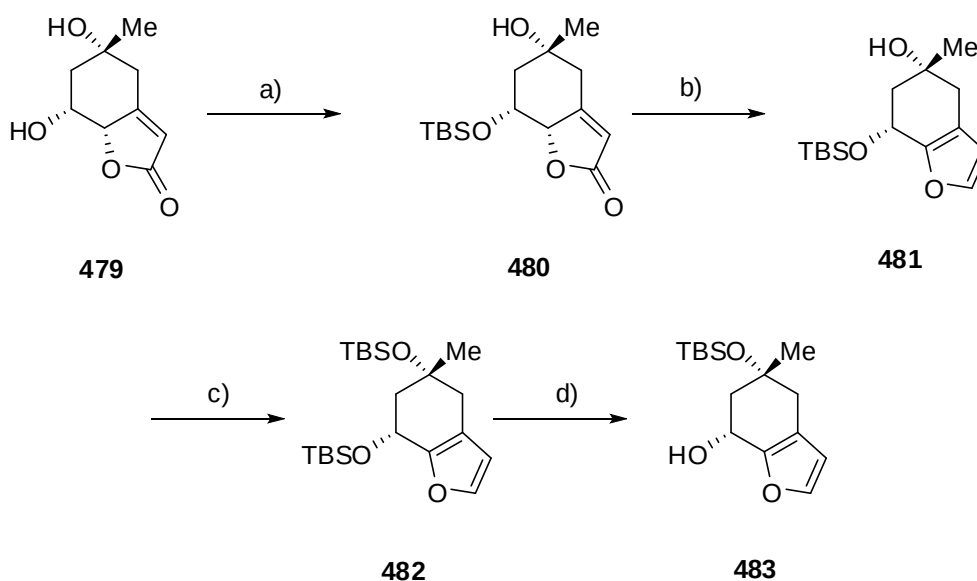
The successful route to this furan started with (*S*)-quinic acid (**472**). This was transformed into butenolide **479** in nine steps (Scheme 160). Key transformations include a reduction-periodate cleavage sequence to convert carboxylic acid **472** into ketone **473**, which was subsequently treated with methyllithium in order to re-establish the tertiary alcohol **474**, a *Z*-selective Peterson olefination to install the α , β -unsaturated ester **478** and trifluoroacetic acid-induced deprotection and cyclisation to yield the target butenolide **479**.



Reagents and conditions: a) $(\text{H}_3\text{CCO})_2$, CSA, $\text{CH}(\text{OMe})_3$, MeOH, 87%; b) i) NaBH_4 , MeOH; ii) NaIO_4 , THF/ H_2O , 90%; c) MeLi, THF, -78°C to rt, 80%; d) aq. HCl, MeOH; e) aq. HCl, Me_2CO , 85%; f) PCC, CH_2Cl_2 , 81%; g) TES-OTf, $i\text{-PrNEt}_2$, CH_2Cl_2 , 83%; h) Cy_2NLi , $\text{TMSCH}_2\text{CO}_2\text{Et}$, THF, -78°C to rt, 99% (5.6 : 1, *Z* : *E*); i) TFA, H_2O , 63% **479**, 15% **480**

Scheme 160: The Conversion of Quinic Acid **472** into Butenolide **479**

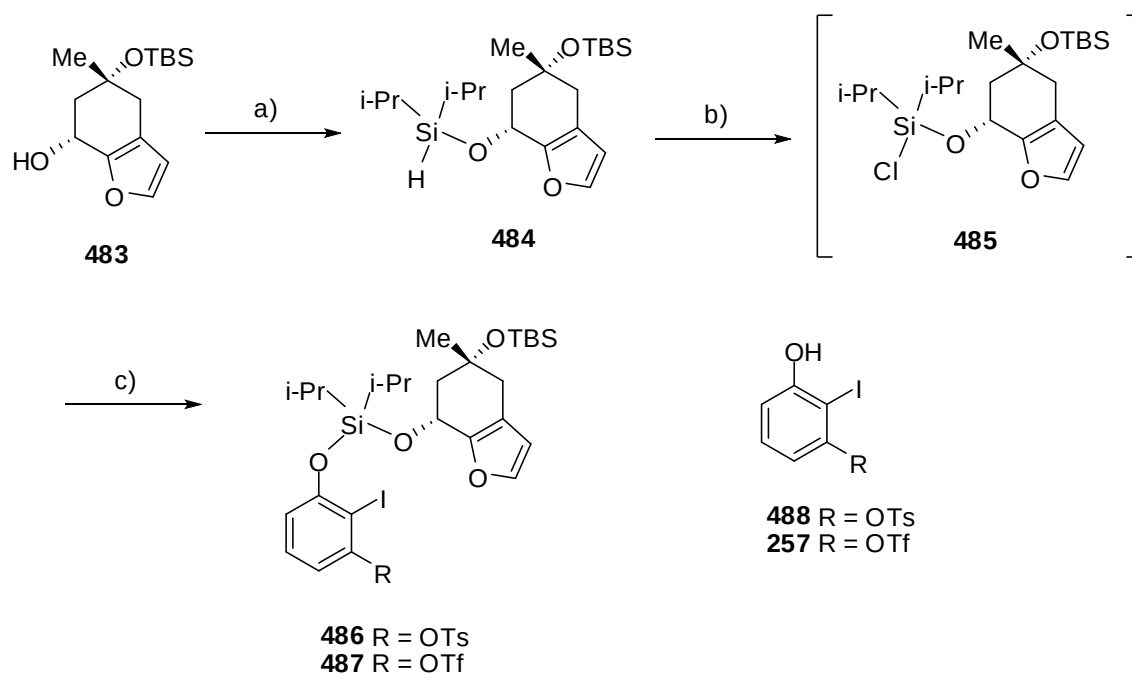
The butenolide was then protected at the secondary alcohol as the silyl ether, before aromatising the butenolide motif into the corresponding furan **481** via the lactol, using catalytic cerium trichloride and di-*iso*-butylaluminum hydride. This could be protected at the tertiary alcohol as the TBS ether before being selectively deprotected at the secondary alcohol to yield furan **483** (Scheme 161).



Reagents and conditions: a) imidazole, DMAP, TBS-Cl, DMF, 90%; b) CeCl_3 , DIBAL-H, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 89%; c) TBS-OTf, $i\text{-PrNEt}_2$, CH_2Cl_2 , 97%; d) TBAF, THF, 71%

Scheme 161: The Conversion of Butenolide **479** into Furan **483**

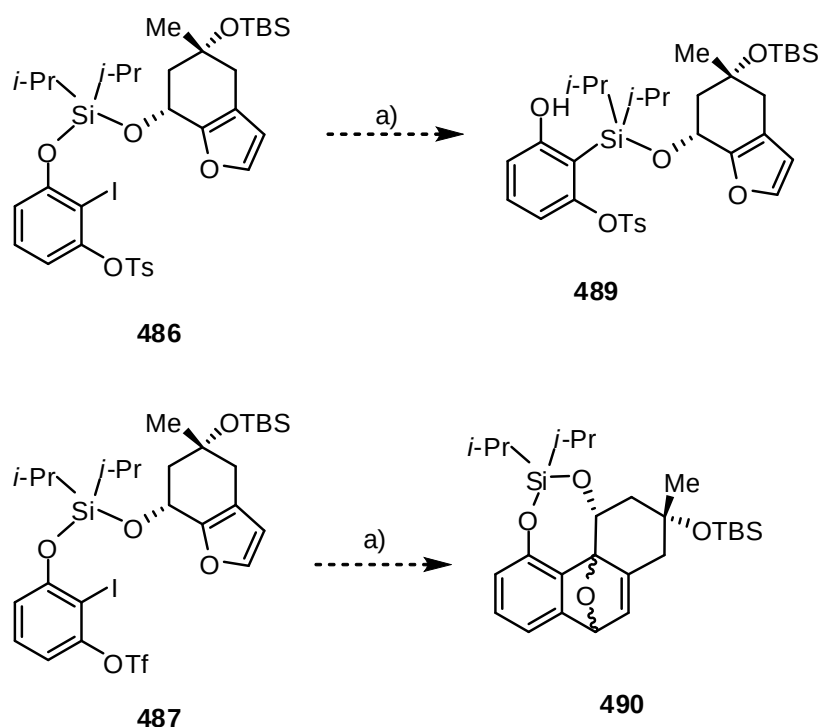
With furan **483** in hand, the synthesis of the silicon linker was examined. After extensive experimentation, the silaketal linker gave the most promising results, and could be reliably synthesised from the reaction of one component (in this case, the furanol) with a dialkylchlorosilane to give silane **484**. The key transformation was the smooth conversion of this silane into the silyl chloride **485** with palladium chloride and hexachloroethane in high yield. This then was treated with the relevant phenol to deliver the silaketals **486** and **487** (Scheme 162).



Reagents and conditions: a) imidazole, $i\text{-Pr}_2\text{Si}(\text{H})\text{Cl}$, CH_2Cl_2 , 94%; b) PdCl_2 , hexachloroethane, 4 Å MS, THF; c) imidazole, **488** or **257**, 4 Å MS, THF, **486** 66%, **487** 76%

Scheme 162: The Synthesis of a Model System for the Development of the Intramolecular Aryne-Furan Cycloaddition

The intramolecular aryne-furan cycloaddition is currently being investigated. For the tosylate, neither the cycloadduct nor starting material are recovered with either set of conditions, possibly due to the elimination of the metal tosylate being slower than migration of silicon from oxygen to carbon, and so the major product is the *o*-silylated phenol **489**. However, the use of the tosylate was not further investigated as the triflate **487** gave the desired cycloadduct **490**. This reaction is currently being optimised, though the yields are already promisingly high, over 75% (Scheme 163). The stereochemistry of the cycloadduct is also being elucidated, with derivatisation to a suitable crystalline structure for X-ray analysis.



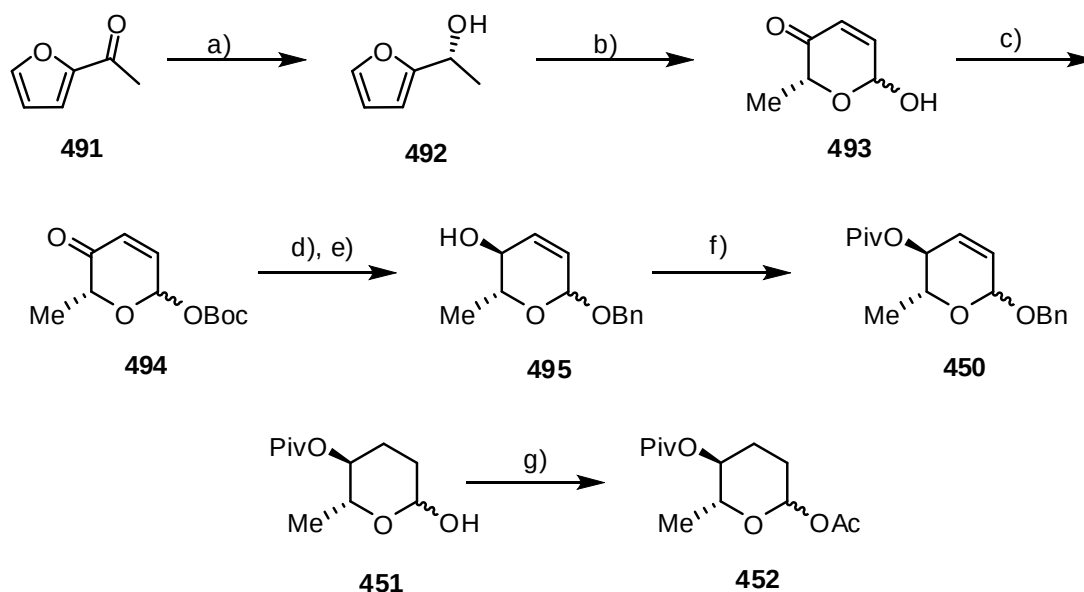
Reagents and conditions: a) *i*-PrMgCl, THF, -78°C to rt or *n*-BuLi, THF, -78°C to rt

Scheme 163: Intramolecular Diels-Alder Reaction Cycloaddition on Aryne Precursors **486** and **487**

7.3 Future Work Towards the Synthesis of Sch 47554 and Sch 47555

Although a route to the pivalate sugar **452** is already described, a couple of the steps suffer from modest yields and more efficient routes could be examined. One route that is worthy of investigation is described in Scheme 163. The synthesis of allylic alcohol **495** is previously described in the literature in a five step route.¹⁷³ This comprises of asymmetric reduction of ketone **491** to alcohol **492**, Achmatowicz reaction using NBS to obtain the pyranone **493**, which is then converted into the corresponding *tert*-butyl carbonate **494**, and from that to the corresponding benzyl ether with palladium catalysis. This compound can then be reduced to give the allylic alcohol **495**.

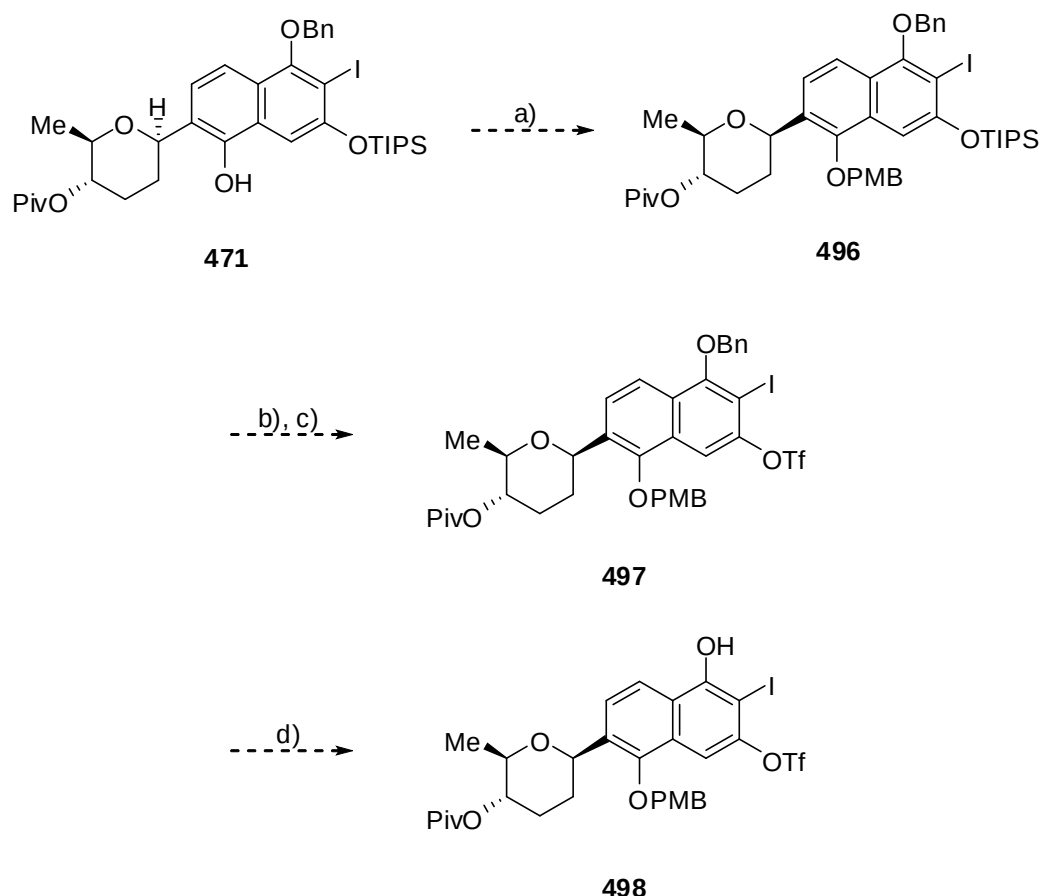
From here, the alcohol can be protected as the pivalate ester, and after hydrogenolysis of the benzyl ether with concomitant alkene hydrogenation lactol **451** is yielded. This intermediate, synthesised previously, can then be acetylated to give the glycosyl acetate **452** in an alternative and potentially higher-yielding synthesis (Scheme 164).



Reagents and conditions: a) $[\text{RuCl}_2(\eta^6\text{-p-cymene})]_2$, (*R,R*)-TsDPEN, H_2O , Et_3N , HCO_3H ; b) NBS, NaOAc , NaHCO_3 , $\text{THF} / \text{H}_2\text{O}$; c) Boc_2O , DMAP; d) BnOH , $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$, PPh_3 , CH_2Cl_2 ; e) NaBH_4 , CeCl_3 , THF / MeOH ; f) imidazole, DMAP, Piv-Cl, CH_2Cl_2 ; g) $\text{Pd}(\text{OH})_2/\text{C}$, H_2 , EtOH/EtOAc ; h) Ac_2O , $\text{C}_5\text{H}_5\text{N}$, CH_2Cl_2 .

Scheme 164: Alternative Synthesis of Glycosyl Acetate 452

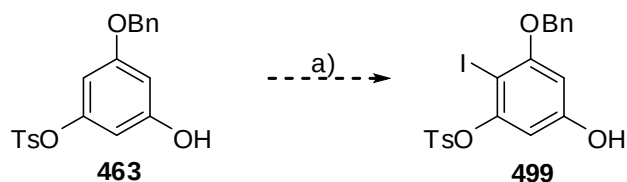
With optimisation of the C-glycosidation of naphthol **470** underway, the next steps of the synthesis of the aromatic core should be investigated. These are mainly standard functional group interconversions, namely PMB-protection of **471** (or another suitable protecting group), conversion of the silyl ether **496** into the corresponding triflate **497** and then debenzoylation to reveal the naphthol **498** (Scheme 165). This can then be attached to the furan moiety with a silaketal tether.



Reagents and conditions: a) PMB-Cl, TBAI, THF; b) TBAF, THF; c) TiF_2O , *i*-PrNEt₂, CH_2Cl_2 , d) H_2 , Pd/C, aq. HCl, EtOAc.

Scheme 165: Completion of the Synthesis of Naphthol **498**

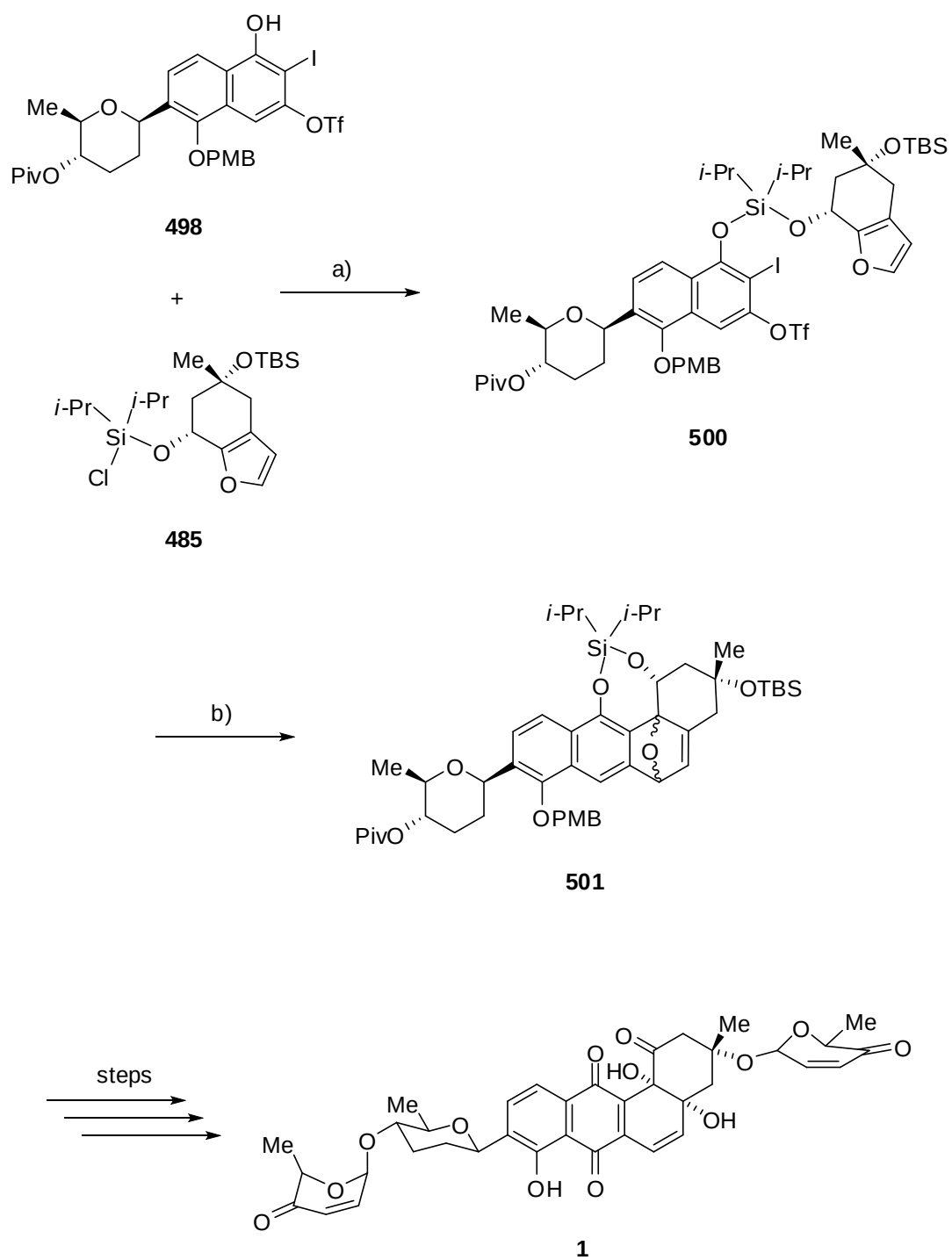
If the final step, namely debenzoylation in the presence of the aryl iodide, does prove to be problematic on this substrate, alternative routes can be investigated. It was found that when phenol **463** was treated with iodine monochloride in the presence of indium triflate, a major product was formed, the spectra of which are consistent with iodide **499**, though after chromatography the product was not sufficiently pure to characterise and insufficient time remained to optimise this (Scheme 166). However, if further analysis were to indicate the iodination did occur as shown, the route is worth further investigation as it would achieve the goal that was targeted previously for obtaining a mono-iodinated substrate.



Reagents and conditions: a) In(OTf)₃, ICl in CH₂Cl₂, MeCN

Scheme 166: Selective Iodination of Phenol **463**

Additionally, with naphthol **498** in hand once the glycosidation is optimised, the remaining steps in the construction of the carbon skeleton of the agylcone can be undertaken. Naphthol **498** will be condensed with silyl chloride **485**, which has already synthesised within the group (Scheme 162) to form key intermediate silaketal **500**. The intramolecular Diels-Alder reaction can then be undertaken on this substrate in order to obtain cycloadduct **501**. This species has the entire carbon framework necessary for the agylcone of the target molecules, Sch 47554 and Sch 57555 and with further elaboration of the oxidation states, functional group interconversions and attachment of the *O*-glycosides, the total synthesis of Sch 47554 (**1**) and Sch 4755 (**2**) can be completed (Scheme 167).



Reagents and conditions: a) imidazole, 4Å MS, THF; b) *i*-PrMgCl, THF, -78 °C to rt

Scheme 167: Completion of the Synthesis of Sch 47554 (**1**) from Naphthol **498** and Silyl Chloride **485**

Experimental Section

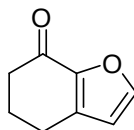
General Experimental Procedures

Melting points were obtained on a Reichert-Thermovar melting point apparatus and are uncorrected. Optical rotations were recorded at 25 °C on a Perkin-Elmer 241 polarimeter with a path length of 1 dm, using the 589.3 nm D-line of sodium. Concentrations (c) are quoted in g/100 mL. Infrared spectra were recorded on a Perkin Elmer Spectrum BX II FT-IR System with ATR technique. Samples were prepared as thin films on the diamond; solid samples were pressed on the diamond. Reported absorptions are strong or medium strength unless stated otherwise and given in wavenumbers (cm⁻¹). ¹H NMR, ¹³C NMR and ¹⁹F NMR spectra were recorded on a Bruker 400 spectrometer operating at 400, 100, 150 MHz respectively. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to a residual solvent peak. CDCl₃ (δ_H: 7.26, δ_C: 77.16), MeOD-*d*₄ (δ_H: 3.31, δ_C: 49.05), acetone-*d*₆ (δ_H: 2.05, δ_C: 30.83). Coupling constants (*J*) are quoted in Hertz (Hz) to the nearest 0.1 Hz. Low and high resolution mass spectrometry (EI, CI, ESI) were recorded by the Imperial College London Department of Chemistry Mass Spectrometry Service using a Micromass Platform II and Micromass AutoSpec-Q spectrometer. Elemental analyses were determined by the University of North London Analytical Service.

All manipulations of air- or moisture-sensitive materials were carried out in oven-dried glassware under an inert atmosphere of nitrogen or argon. Reaction solvents were distilled from CaH₂ (dichloromethane, methanol, pyridine), Na (toluene), Na/Ph₂CO (tetrahydrofuran, diethyl ether) or obtained as dry or anhydrous from Sigma-Aldrich or Acros Organics (*N,N*-dimethylformamide, triethylamine, acetonitrile, *tert*-butanol). Other solvents and all reagents were obtained from commercial suppliers (Sigma-Aldrich; Acros Organics, Alfa Aesar, FluoroChem) and were used as obtained unless otherwise stated. *n*-Butyllithium, *sec*-butyllithium and *tert*-butyllithium were titrated against diphenylacetic acid following the method of Kofron¹⁷⁴ to determine its concentration. *iso*-Propylmagnesium chloride was titrated against salicylaldehyde phenylhydrazone following the method of Love¹⁷⁵ to determine its concentration.

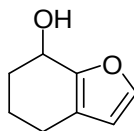
All flash column chromatography was carried out on BDH silica gel 60, particle size 0.040 – 0.063 mm unless otherwise stated. Thin-layer chromatography (TLC) was performed on pre-coated glass-backed plates (Merck Kieselgel 60 F₂₅₄), and visualised with ultraviolet light (366 nm and 254 nm), vanillin, potassium permanganate (KMnO₄) or phosphomolybdic acid (PMA) stains as deemed appropriate.

4,5-Dihydrobenzofuran-7-one (263)¹³⁵



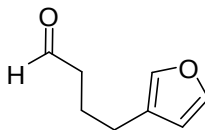
An aqueous solution of cyclohexane-1,2-dione (4.50 g, 40.1 mmol in 20 mL) was added dropwise to an aqueous solution of chloroacetaldehyde (50% w/w, 12.4 mL, 63.0 mmol) and sodium hydrogen carbonate (5.80 g, 69.0 mmol) in water (45 mL), at 0 °C, before being warmed to room temperature, and stirred for a further 14 hours. After this time, ethyl acetate (60 mL) was added, and the pH made to 1, using 10% sulfuric acid. This solution was stirred for a further 90 minutes, before being neutralised with solid sodium hydrogen carbonate. The organic phase was separated, washed with brine (50 mL), dried over magnesium sulfate, concentrated under reduced pressure and chromatographed (3:2, hexanes/ethyl acetate) to yield the title product as an off-white crystalline solid (3.20 g, 39%); R_f : 0.52 (3:2, hexanes/ethyl acetate); mp: 47-49 °C (hexanes/ethyl acetate), lit.:¹³⁵ 49 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.58 (d, J = 1.6 Hz, 1H, Ar-*H1*), 6.43 (d, J = 1.6 Hz, 1H, Ar-*H2*), 2.80 (t, J = 6.0 Hz, 2H, - CH_2 -, H6), 2.60 (t, J = 6.0 Hz, 2H, - CH_2 -, C4), 2.18 (qt., J = 6.0 Hz, 2H, - CH_2 -, C5); ^{13}C NMR (100 MHz, CDCl_3) δ 186.40, 147.52, 140.29, 118.66, 111.59, 38.21, 24.39, 22.93; MS (CI, NH_3), 154 $[\text{M} + \text{NH}_4]^+$.

4,5,6,7-Tetrahydrobenzofuran-7-ol (264)¹³⁵



A solution of lithium aluminium hydride (1 M in THF, 13.1 mL, 13.1 mmol) was added dropwise to a solution of **263** (1.42 g, 10.5 mmol) in THF (3 mL) at 0 °C. Upon completion, the solution was warmed to room temperature over 1 hour. After this time, the reaction was quenched by the addition of 2 M sodium hydroxide and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was chromatographed (1:1 hexanes/ethyl acetate) to yield the title product as a very pale yellow oil (756 mg, 53%); R_f : 0.48 (1:1 diethyl ether / hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.29 (d, J = 1.6 Hz, 1H, Ar-*H*), 6.20 (d, J = 1.6 Hz, 1H, Ar-*H*), 4.74 (m, 1H, *CHOH*), 2.80 (br. s, 1H, CH-OH), 2.57-2.50 (m, 1H, -CH-), 2.45-2.37 (m, 1H, -CH-), 1.88 – 1.71 (m, 4H, CH_2CH_2); ^{13}C NMR (100 MHz, CDCl_3) δ 151.00, 141.99, 120.42, 110.25, 62.39, 32.51, 22.52, 19.20; MS (CI, NH_3), 156 $[\text{M} + \text{NH}_4]^+$.

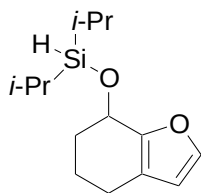
4-(Furan-3-yl)butanal (**283**)¹³⁷



Hydrazine (1.69 mL, 54 mmol) was added to a solution of 3-furaldehyde **280** (4.26 mL, 50 mmol) in ethylene glycol (110 mL) and the resulting mixture was stirred for 15 minutes in a vessel equipped with a short-path distillation head. After this time, potassium hydroxide (7.43 g, 132 mmol) was added and the resulting mixture was heated to 150 °C. Vigorous gas evolution was observed from 130 °C and the distillate was collected. The organic layer was separated from the lower aqueous layer to give a product consisting of dihydrofuran **281** and furan **282** (4.83 g, 2.7:1, 54% of **281**).

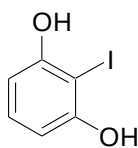
Acrolein (11.0 mL, 165.6 mmol) was added to a solution of the dihydrofuran **281**/furan **282** mixture (4.83 g) in dichloromethane (400 mL) and the mixture was heated under reflux for 15 hours, before being allowed to cool and concentrated under reduced pressure. The resulting residue was purified by distillation (92 °C, < 20 Torr) to yield the title product as a colourless oil (3.35 g, 73%); R_f : 0.77 (4:1 hexanes/ethyl acetate); IR: $\nu_{\max}$ 2939, 2724, 1722, 1024, 873, 782; ^1H NMR (400 MHz, CDCl_3): δ 9.79 (br. s, 1H, -CHO), 7.38 (t, $J = 1.2$ Hz, 1H, Ar-*H*), 7.24 (br. s, 1H, Ar-*H*), 6.28 (br. s, 1H, Ar-*H*); 2.51-2.47 (m, 4H, OHC- CH_2 - and Ar- CH_2 -), 1.92 (qn., $J = 7.4$ Hz, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$ -); ^{13}C NMR (400 MHz, CDCl_3) δ 202.24, 143.00, 139.09, 123.95, 110.78, 43.18, 24.03, 22.33; MS (CI, NH_3) m/z : 138 $[\text{M}]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_8\text{H}_{10}\text{O}_2$: 138.0681 $[\text{M}]^+$, found: 138.0683 $[\text{M}]^+$; Elem. Anal. calc. for $\text{C}_8\text{H}_{10}\text{O}_2$: C 69.54%, H 7.30%, found: C 69.49%, H 7.20%.

Diisopropyl(4,5,6,7-tetrahydrobenzofuran-7-yloxy)silane (289)



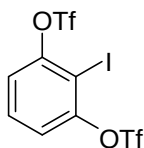
Di-iso-propylchlorosilane (341 μ L, 301 mg, 2.0 mmol) was added slowly to a solution of alcohol **264** (276 mg, 2.0 mmol), diisopropylethylamine (383 μ L, 284 mg, 2.2 mmol) and DMAP (24 mg, 0.2 mmol) in dichloromethane (5 mL) and the resulting mixture was stirred for 3 hours. After this time, the mixture was quenched with water (10 mL), diluted with dichloromethane (5 mL) and the organic phase was washed with brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and chromatographed (14:1 hexanes/ethyl acetate) to give the title product (361 mg, 71%) as a colourless oil; R_f : 0.95 (14:1 hexanes/ethyl acetate); IR: $\nu_{\max}$ 2942, 2863, 2096, 1461; ^1H NMR (400 MHz, CDCl_3) δ 7.31 (d, J = 2.0 Hz, 1H, Ar- H), 6.21 (d, J = 2.0 Hz, 1H, Ar- H), 4.81 (t, J = 4.0 Hz, 1H, -C(H)OSi), 4.28 (s, 1H, OSi- H), 2.56-2.34 (m, 2H, CH_2), 2.01-1.69 (m, 4H, CH_2), 1.40-1.00 (m, Si- $\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 151.11, 141.57, 119.86, 110.11, 65.23, 33.06, 22.31, 19.10, 17.45, 12.81; MS (CI, NH_3) m/z : 253 $[\text{M}+\text{H}]^+$, 121 $[\text{C}_8\text{H}_8\text{O}+\text{H}]^+$, 138 $[\text{C}_8\text{H}_8\text{O}_2+\text{H}]^+$; Elem. Anal. calc. for $\text{C}_{14}\text{H}_{24}\text{O}_2\text{Si}$: C 66.61% H 9.58%, found: C 66.57% H: 9.48%.

2-Iodoresorcinol (255)¹³³



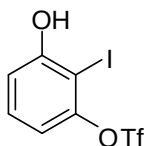
Sodium hydrogen carbonate (8.30 g, 98.9 mmol) was added portionwise to an aqueous solution of resorcinol (9.90 g, 90.0 mmol in 90 mL) and iodine (23.95 g, 94.4 mmol) at 0 °C, with vigorous stirring. The solution was allowed to warm to room temperature over the course of 20 minutes and stirred at this temperature for a further 10 minutes. The mixture was extracted with diethyl ether (3 x 100ml), dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue was then taken up in chloroform (100 mL) and concentrated under reduced pressure. The resulting solid was triturated in chloroform at –10 °C for 1 hour and isolated by vacuum filtration to yield the title compound as a white solid (15.00 g, 71%); mp 90-91 °C, lit.:¹³³ 91-93 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.04 (s, 2H, Ar-OH), 6.94 (t, 1H, *J* = 8.0 Hz, Ar-*H*), 6.34 (d, 2H, *J* = 8.0 Hz), ¹³C NMR (100 MHz, *d*⁶-DMSO) δ 158.49, 129.70, 106.19, 75.59; MS (CI, NH₃) *m/z* 254 [M+NH₄]⁺.

2-Iodo-1,3-phenylene bis(trifluoromethanesulfonate) (256) ¹³³



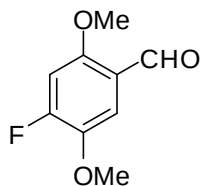
Triflic anhydride (20.4 mL, 121 mmol) was added to a suspension of 2-iodoresorcinol **255** (13.00 g, 55.1 mmol) in dichloromethane (130 mL) and di-*iso*-propylethylamine (23.0 mL, 132 mmol) at $-78\text{ }^{\circ}\text{C}$, and then allowed to warm to room temperature over the course of 90 minutes. After this time, the mixture was slowly quenched with water (100 mL) and the organic phase was washed with water (3 x 50 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (9:1 dichloromethane/hexanes) to yield the title compound as an off-white solid (25.94 g, 94%); R_f : 0.13 (hexanes); mp $34\text{--}35\text{ }^{\circ}\text{C}$ (hexane), lit.:¹³³ $34.3\text{--}36.2\text{ }^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.59 (t, 1H, $J = 8.4\text{ Hz}$, Ar-*H*), 7.41 (d, 1H, $J = 8.4\text{ Hz}$, Ar-*H*); ^{13}C NMR (100 MHz, CDCl_3) δ 151.6, 131.0, 121.5, 118.7 (q, $J_{\text{C-F}} = 316\text{ Hz}$), 87.7; MS (CI, NH_3) m/z 518 $[\text{M}+\text{NH}_4]^+$.

3-Hydroxy-2-iodophenyl trifluoromethanesulfonate (257)¹³³



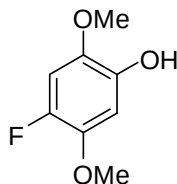
Caesium carbonate (4.89 g, 15.0 mmol) was added to a solution of **256** (5.00 g, 10.0 mmol) in dimethoxyethane (30 mL), and the resulting suspension was heated under reflux for 3 hours, after which time the mixture was cooled, saturated aqueous ammonium chloride was added (35 mL) and the mixture was extracted with diethyl ether (2 x 40 mL). The organic phase was washed with brine (40 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (9:1, hexanes/dichloromethane) to yield the title product as a colourless oil (3.09 g, 84%); R_f : 0.45 (9:1 dichloromethane/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.34 (t, 1H, $J = 8.0$ Hz, Ar-*H*), 7.03 (d, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz, Ar-*H*), 6.95 (d, 1H, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz, Ar-*H*), 5.68 (br. s, Ar-OH); ^{13}C NMR (100 MHz, CDCl_3) δ 157.18, 150.28, 130.73, 118.7 (q, $J_{\text{C-F}} = 318$ Hz), 114.68, 114.04, 81.94; MS (CI, NH_3) m/z : 386 $[\text{M}+\text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_7\text{H}_8\text{F}_3\text{INO}_4\text{S}$ $[\text{M}+\text{NH}_4]^+$: 385.9171, found: 385.9179.

4-Fluoro-2,5-dimethoxybenzaldehyde (**269**)¹³⁶



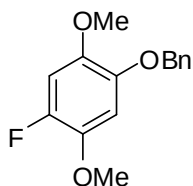
Tin tetrachloride (15.5 mL, 132 mmol) was added dropwise to a solution of dimethoxyfluorobenzene **100** (10.32 g, 66.1 mmol) in dry dichloromethane (50 mL) at 0 °C. Methyl dichloromethyl ether (14.9 mL, 165 mmol) was subsequently added dropwise to the resulting mixture, at 0 °C rapidly turning the solution from orange to dark green. The resulting mixture was allowed to warm to room temperature over 30 minutes. After this time, concentrated hydrochloric acid (20 mL) and ice (140 g) were added, and the mixture stirred vigorously for a further 90 minutes, adopting a turquoise colour in the process. After this time, the mixture was separated, and the organic phase was washed with 1 M hydrochloric acid (50 mL), water (50 mL), 1 M sodium hydroxide (2 x 50 mL), brine (50 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting solid was recrystallised from ethanol to afford the title compound as white crystals (10.21 g, 84 %); R_f : 0.50 (dichloromethane); mp 98-100 °C (ethanol), lit.¹³⁶ 99-100 °C; IR: $\nu_{\max}$ 2984, 2872, 1673, 1500, 1412, 1217, 1207, 1025, 877; ^1H NMR (400 MHz, CDCl_3) δ 10.35 (s, 1H, Ar-CHO), 7.43 (d, 1H, $J_{\text{H-F}} = 9.6$ Hz, Ar-H6), 6.78 (d, 1H, $J_{\text{H-F}} = 12.4$ Hz, Ar-H3), 3.89 (s, 3H, Ar-OCH₃) ; 3.88 (s, 3H, Ar-OCH₃); ^{13}C NMR (100 MHz, CDCl_3) δ 188.11, 157.40 (d, $J_{\text{C-F}} = 9.1$ Hz), 157.30 ($J_{\text{C-F}} = 258$ Hz), 142.19 (d, $J_{\text{C-F}} = 11.2$ Hz), 120.64 (d, $J_{\text{C-F}} = 2.9$ Hz), 111.96 (d, $J_{\text{C-F}} = 2.5$ Hz), 101.36 (d, $J_{\text{C-F}} = 22.5$ Hz), 56.61, 56.35; MS (CI, NH_3) m/z : 202 [$\text{M}+\text{NH}_4$]⁺; HRMS (CI, NH_3) m/z calc. for $\text{C}_9\text{H}_{10}\text{O}_3\text{F}$: 185.0611 [$\text{M} + \text{H}$]⁺, found: 185.0611.

4-Fluoro-2,5-dimethoxyphenol (270)



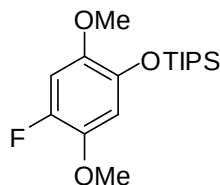
A solution of aldehyde **269** (11.09 g, 60.0 mmol in 85 mL) in dichloromethane (40 mL) was added to a solution of 3-chloroperoxybenzoic acid (77% w/w, 31.06 g, 180 mmol) in dichloromethane (60 mL), and the mixture stirred at room temperature for 5 hours. After this time, the mixture was filtered and the filtrate was concentrated under reduced pressure to yield the crude formyl ester as a solid. This residue was dissolved in a solution of sodium hydroxide (4.8 g) in 1:1 ethanol/water (100 mL), and the mixture was stirred for 2 hours, before being neutralised with 2 M hydrochloric acid (*ca.* 100 mL). The mixture was extracted with dichloromethane (3 x 150 mL), and the organic phase was washed with saturated aqueous sodium hydrogen carbonate (50 mL), water (50 mL), brine (50 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (dichloromethane) to yield the title compound as a white crystalline solid (8.06 g, 78%); R_f : 0.51 (dichloromethane); mp 75-76 °C (hexane); IR: $\nu_{\max}$ 3481, 2950, 2851, 1663, 1598, 1516, 1192, 1030, 851; ^1H NMR (400 MHz, CDCl_3) δ 6.73 (d, 1H, $J_{\text{H-F}}$ = 12.0 Hz, Ar-*H*3), 6.67 (d, 1H, $J_{\text{H-F}}$ = 8.4 Hz, Ar-*H*6), 5.41 (br. s, 1H, Ar-OH), 3.86 (s, 3H, Ar-OCH₃), 3.85 (s, 3H, Ar-OCH₃); ^{13}C NMR (100 MHz, CDCl_3) δ 146.95, 144.59, 141.423 (d, $J_{\text{C-F}}$ = 46.8 Hz), 139.62 (d, $J_{\text{C-F}}$ = 32.0 Hz), 101.769, 100.88 (d, $J_{\text{C-F}}$ = 95.2 Hz), 57.07, 56.70; MS (CI, NH_3) m/z : 190 $[\text{M}+\text{NH}_4]^+$ 172 $[\text{M}+\text{H}]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_8\text{H}_9\text{FO}_3$ $[\text{M} + \text{NH}_4]^+$: 190.0879, found 190.0880; Elem. Anal. calc. for $\text{C}_8\text{H}_9\text{FO}_3$: C 55.81%, H 5.27%, found: C 55.79%, H 5.30%.

1-(Benzyloxy)-2,5-dimethoxy-4-fluorobenzene (317)



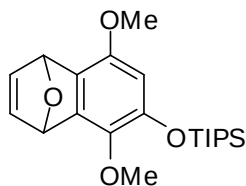
Benzyl bromide (2.3 mL, 29.2 mmol) was added to a suspension of **270** (3.50 g, 22.4 mmol) and potassium carbonate (4.65 g, 33.7 mmol) in dry DMF (30 mL), and the resulting mixture was heated at 80 °C for 2 hours, after which time the suspension was cooled to 50 °C, and distilled water (10 mL) was added over the course of 30 minutes, resulting in the precipitation of a white solid. The precipitate was collected by vacuum filtration and recrystallised from chloroform/methanol, to yield the title compound as a white solid (5.44 g, 93%); R_f : 0.65 (dichloromethane); mp 86-87 °C (chloroform/methanol); IR: $\nu_{\max}$ 2972, 2948, 1519, 1456, 1215, 1188, 1035, 985, 820, 698; ^1H NMR (400 MHz, CDCl_3) δ 7.46-7.33 (m, 5H, Ph-*H*) 6.75 (d, 1H, $J_{\text{H-F}}$ = 12.4 Hz, Ar-*H*3), 6.63 (d, 1H, $J_{\text{H-F}}$ = 8.4 Hz, Ar-*H*6), 5.11 (s, 2H, OCH_2Ph), 3.85 (s, 3H, ArOCH_3), 3.79 (s, 3H, ArOCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 147.2 ($J_{\text{C-F}}$ = 238 Hz), 144.1 (d, $J_{\text{C-F}}$ = 28.3 Hz), 143.93, 140.53 (d, $J_{\text{C-F}}$ = 44.8 Hz), 137.01, 128.59, 128.04, 127.58, 105.47, 104.48, 102.18 (d, $J_{\text{C-F}}$ = 92.4 Hz), 72.48, 57.56, 56.73; MS (CI, NH_3) m/z : 280 $[\text{M}+\text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{15}\text{H}_{19}\text{FNO}_3$ $[\text{M} + \text{NH}_4]^+$: 280.1349, found 280.1348; Elem. Anal. calc. for $\text{C}_{15}\text{H}_{15}\text{FO}_3$: C 68.69%, H 5.76%, found: C 68.81%, H 5.76%.

2,5-Dimethoxy-4-(tri-*iso*-propylsiloxy)fluorobenzene (321)



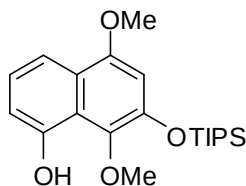
Tri-*iso*-propylsilyl triflate (11.6 mL, 43.0 mmol) was added dropwise to a solution of triethylamine (8.0 mL, 57.3 mmol) and **270** (7.05 g, 41.0 mmol) in dichloromethane (100 mL) at 0 °C, and the solution was stirred for 1 hour at room temperature. After this time, the mixture was quenched with saturated aqueous ammonium chloride (50 mL) and the mixture extracted into diethyl ether. The organic phase was washed with brine, dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (8:1 hexanes/ethyl acetate) to yield the title compound as a colourless oil (12.04 g, 89%); R_f : 0.82 (dichloromethane); IR (neat) $\nu_{\max}$ (cm⁻¹) : 2945, 2867, 1517, 1450, 1401, 1222, 1203, 1040, 907; ¹H NMR (400 MHz, CDCl₃) 6.68 (d, J_{H-F} = 12.8 Hz, 1H, Ar-*H*3), 6.59 (d, J_{H-F} = 8.4 Hz, 1H, Ar-*H*6), 3.83 (s, 3H, Ar-OCH₃), 3.76 (s, 3H, Ar-OCH₃), 1.26 (m, 3H, Si-CH(CH₃)₂), 1.11 (d, 18H, Si-CH(CH₃)₂) ¹³C NMR (100 MHz, CDCl₃) δ 146.81 (J_{C-F} = 237 Hz), 144.54 (d, J_{C-F} = 8.0 Hz), 141.21, 140.57 (d, J_{C-F} = 10.8 Hz), 107.91, 101.95 (d, J_{C-F} = 23.0 Hz), 57.35, 56.25, 17.88, 12.83; MS (CI, NH₃) m/z : 329 [M + H]⁺; Elem. Anal. calc. for C₁₇H₁₉FO₃Si: C 62.16%, H 8.90%, found: C 62.18%, H 8.97%.

(3,6-Dimethoxy-11-oxa-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5,9-tetraen-4-yloxy)-tri-*iso*-propyl-silane (324)



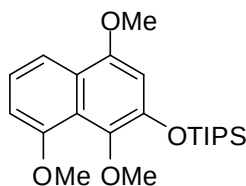
A solution of *tert*-butyllithium (1.30 M in pentane, 2.3 mL, 3.0 mmol) was added dropwise to a solution of **321** (984 mg, 3.0 mmol) in THF (10 mL), at -78°C , and stirred at this temperature for 30 minutes. After this time, furan (1.1 mL, 15.0 mmol) was added and the resulting solution was allowed to warm to room temperature over 2 hours, before being quenched with water (10 mL). Diethyl ether (25 mL) was added and the organic phase was washed with brine (20 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (8:1 hexanes/ethyl acetate) to give the title product as a waxy solid (845 mg, 75%); R_f : 0.41 (14:1 hexanes/ethyl acetate); mp $40\text{--}41^{\circ}\text{C}$ (ethyl acetate/hexane); IR: ν_{max} 2944, 2866, 1614, 1486; ^1H NMR (400 MHz, CDCl_3) δ 7.08 (dd, $J_1 = 5.6$ Hz, $J_2 = 1.6$ Hz, 1H, $\text{CH}=\text{CH}$), 7.02 (dd, $J_1 = 5.6$ Hz, $J_2 = 1.6$ Hz, 1H, $\text{CH}=\text{CH}$), 6.15 (s, 1H, Ar-*H*), 5.93 (d, $J = 13.2$ Hz, 2H, HC-O), 3.83 (s, 3H, Ar- OCH_3), 3.77 (s, 3H, Ar- OCH_3), 1.29 (sep., $J = 7.2$ Hz, 3H, $-\text{Si}(\text{CH}(\text{CH}_3)_2)$), 1.13 (d, $J = 7.2$ Hz, 18H, $-\text{Si}(\text{CH}(\text{CH}_3)_2)$); ^{13}C NMR (100 MHz, CDCl_3) 148.26, 147.60, 143.33, 141.84, 141.05, 140.44, 127.16, 103.08, 80.77, 80.22, 61.20, 56.38, 17.92, 12.80; MS (CI, NH_3) m/z : 377 $[\text{M}+\text{H}]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{21}\text{H}_{32}\text{O}_4\text{Si}$ $[\text{M} + \text{H}]^+$: 377.2148, found 377.2148; Elem. Anal. calc. for $\text{C}_{21}\text{H}_{32}\text{O}_4\text{Si}$: C 66.98%, H 8.57%, found: C 67.05%, H 8.57%.

5,8-Dimethoxy-7-(tri-*iso*-propylsiloxy)naphthalen-1-ol (326)



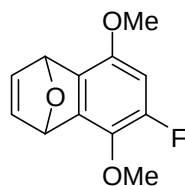
Trifluoroacetic acid (50 μ L) was added to a solution of **324** (533 mg, 1.4 mmol) in dichloromethane (6 mL) and the resulting solution was stirred at room temperature for 90 minutes. After this time, the solution was concentrated under reduced pressure and the resulting residue was chromatographed (8:1 hexanes/ethyl acetate) to yield the title product as an off-white powder (480 mg, 90%); mp 51-54 $^{\circ}$ C (hexanes/ethyl acetate); R_f 0.76 (14 : 1, pentane/ethyl acetate); IR: $\nu_{\max}$ 3345, 2944, 2867, 1612; ^1H NMR (400 MHz, CDCl_3) δ 9.72 (s, 1H, Ar-OH), 7.65 (d, J = 8.4 Hz, 1H, Ar-H4), 7.23 (app. t, J_1 = 8.0 Hz, J_2 = 8.0 Hz, 1H, Ar-H3), 6.90 (d, J = 7.2 Hz, 1H, Ar-H2), 6.50 (s, 1H, Ar-H6), 4.02 (s, 3H, Ar-OCH₃), 3.94 (s, 3H, Ar-OCH₃), 1.35 (sep., J = 7.2 Hz, 3H, -Si(CH(CH₃)₂)), 1.18 (d, J = 7.2 Hz, 18H, Si(CH(CH₃)₂)); ^{13}C NMR (100 MHz, CDCl_3) δ 153.22, 152.56, 143.62, 137.68, 124.71, 123.35, 118.31, 113.03, 111.20, 101.16, 61.83, 55.68, 17.95, 12.98; MS (CI, NH_3) m/z : 377 $[\text{M}+\text{H}]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{21}\text{H}_{32}\text{O}_4\text{Si}$ $[\text{M} + \text{H}]^+$: 377.2148, found 377.2146; Elem. Anal. calc. for $\text{C}_{21}\text{H}_{32}\text{O}_4\text{Si}$: C 66.98% H 8.57%, found: C 66.95% H 8.62%.

Tri-*iso*-propyl(1,4,8-trimethoxynaphthalen-2-yloxy)silane (327)



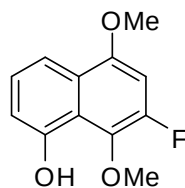
A solution of naphthol **326** (169 mg, 0.5 mmol) in THF (1.5 mL) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 22 mg, 0.5 mmol) in THF (1.5 mL), followed by iodomethane (34 μ L, 68 mg, 0.5 mmol). The resulting mixture was stirred at room temperature for 16 hours. After this time, the reaction was quenched with water (5 mL) and extracted into ethyl acetate (2 x 10 mL). The organic phase was washed with brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (14:1, hexanes/ethyl acetate) to yield the title product as a solid (152 mg, 86%); mp 45-49 °C (hexanes/ethyl acetate); R_f 0.64 (14:1, hexanes/ethyl acetate); IR: $\nu_{\max}$ 2944, 2865, 1598, 1509; ^1H NMR (400 MHz, CDCl_3) δ 7.78 (dd, $J_1 = 8.4$ Hz, $J_2 = 0.8$ Hz, 1H, Ar-*H*5), 7.24 (app. t, $J_1 = 8.4$ Hz, $J_2 = 7.2$ Hz, 1H, Ar-*H*6), 6.88 (app. d, $J = 7.2$ Hz, 1H, Ar-*H*7), 6.58 (s, 1H, Ar-*H*3), 4.00 (s, 3H, Ar- OCH_3), 3.94 (s, 3H, Ar- OCH_3), 3.84 (s, 3H, Ar- OCH_3), 1.37 (sep., $J = 7.2$ Hz, 3H, $-\text{Si}(\text{CH}(\text{CH}_3)_2)$), 1.17 (d, $J = 7.2$ Hz, 18H, $-\text{Si}(\text{CH}(\text{CH}_3)_2)$); ^{13}C NMR (100 MHz, CDCl_3) δ 155.65, 151.63, 146.32, 139.92, 123.52, 121.87, 116.97, 114.52, 107.03, 101.85, 61.60, 56.40, 55.73, 18.05, 12.96; MS (NH_3 , CI) m/z : 391 $[\text{M}+1]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{22}\text{H}_{35}\text{O}_4\text{Si}$ $[\text{M} + \text{H}]^+$: 391.2305, found 391.2307; Elem. Anal. calc. for $\text{C}_{22}\text{H}_{34}\text{O}_4\text{Si}$: C 67.65%, H 8.77%, found: C 67.74%, H 8.70%.

4-Fluoro-3,6-dimethoxy-11-oxa-tricyclo[6.2.1.0^{2,7}]undeca-2(7)-3,5,9-tetraene
(221)¹³⁹



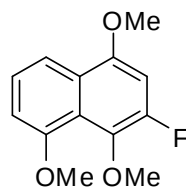
A solution of *n*-butyllithium (1.90 M in hexanes, 36.9 mL, 70.0 mmol) was added dropwise to a solution of difluorobenzene **204** (12.18 g, 70.0 mmol) in THF (230 mL) at -78°C . After stirring for 30 minutes at this temperature, furan (25.5 mL, 350 mmol) was added, and the resulting mixture was warmed to room temperature over a period of 2 hours. Water (200 mL) was then added, and the solution extracted into diethyl ether (2 x 200 mL). The organic phase was washed with brine (200 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (dichloromethane) to yield the title compound as a colourless oil (12.70 g, 82%); R_f : 0.30 (dichloromethane); ^1H NMR (400 MHz, CDCl_3) δ 7.10 (dd, $J_1 = 5.6$ Hz, $J_2 = 1.8$ Hz, 1H, $\text{CH}=\text{CH}$), 7.06 (dd, $J_1 = 5.6$ Hz, $J_2 = 1.8$ Hz, 1H, $\text{CH}=\text{CH}$), 6.39 (d, 1H, $J_{\text{H-F}} = 12.8$ Hz, 1H, Ar-*H*5), 5.98 (br. s, 1H, Ar-*H*1/*H*8), 5.93 (br.s, 1H, Ar-*H*1/*H*8) 3.92 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 153.47 (d, $J_{\text{C-F}} = 246$ Hz), 147.80 (d, $J_{\text{C-F}} = 8.7$ Hz), 143.41, 142.20, 141.6, 136.6 (d, $J_{\text{C-F}} = 14.0$ Hz), 130.89, 99.30 (d, $J_{\text{C-F}} = 24.2$ Hz), 80.87 (d, $J_{\text{C-F}} = 2.5$ Hz), 80.01, 61.56, 56.29; MS (CI, NH_3) m/z : 223 $[\text{M}+\text{H}]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{12}\text{H}_{12}\text{FO}_3$ $[\text{M}+\text{H}]^+$: 223.0770, found: 223.0779.

7-Fluoro-5,8-dimethoxynaphthalen-1-ol (222)¹³⁹



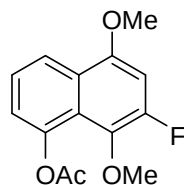
6 M Hydrochloric acid (51 mL) was added to a solution of **221** (9.75 g, 43.7 mmol) in methanol (200 mL) and the mixture was heated under reflux for 3 hours, after which time it was cooled to 0 °C. The precipitate was isolated by vacuum filtration and recrystallised from methanol to yield the title product as a white crystalline solid (8.26 g, 85%); R_f : 0.27 (1:1 hexanes/dichloromethane); mp 70-72 °C (methanol); ^1H NMR (400 MHz, CDCl_3) δ 9.41 (s, 1H, Ar-OH), 7.71 (d, 1H, J = 8.0 Hz, Ar-H4), 7.33 (t, 1H, J = 8.0 Hz, Ar-H3), 6.97 (d, 1H, J = 8.0 Hz, Ar-H2), 6.62 (d, 1H, $J_{\text{H-F}}$ = 8.4 Hz, Ar-H6), 4.13 (s, 3H, ArOCH_3), 3.98 (s, 3H, ArOCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 153.94 (d, $J_{\text{C-F}}$ = 26.8 Hz), 152.75 (d, $J_{\text{C-F}}$ = 40.4 Hz), 151.53, 149.12, 134.81, 126.15, 117.48, 113.33, 112.15, 96.08 (d, $J_{\text{C-F}}$ = 26.7 Hz), 62.89, 55.96; MS (CI, NH_3) m/z : 223 $[\text{M}+\text{H}]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{12}\text{H}_{12}\text{FO}_3$ $[\text{M}+\text{H}]^+$ 223.0770, found: 223.0779.

2-Fluoro-1,4,8-trimethoxynaphthalene (**292**)¹³⁹



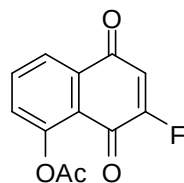
A solution of naphthol **222** (3.37 g, 15.1 mmol) in DMF (30 mL) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 779 mg, 18.9 mmol) in DMF (10 mL) at 0 °C, followed by iodomethane (1.18 mL, 18.9 mmol) and the resulting mixture was stirred at room temperature for 16 hours. After this time, water (20 mL) was carefully added and the solution extracted into ethyl acetate (2 x 20 mL). The organic phase was washed with water (20 mL), brine (20 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (1:1 hexanes/dichloromethane) to deliver the title compound as a white crystalline solid (3.18 g, 90%), R_f : 0.34 (dichloromethane); mp 85-87 °C (ethyl acetate/hexanes), ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, J = 8.8 Hz, 1H, Ar-*H*5), 7.35 (t, J = 8.0 Hz, 1H, Ar-*H*6), 6.95 (d, J = 7.6 Hz, 1H, Ar-*H*7), 6.71 (d, 1H, $J_{\text{C-F}}$ = 12.0 Hz, Ar-*H*3), 4.02 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 156.20 (d, $J_{\text{C-F}}$ = 58.8 Hz), 154.56, 152.51 (d, $J_{\text{C-F}}$ = 37.6 Hz), 135.90 (d, $J_{\text{C-F}}$ = 54.8 Hz), 125.02, 124.68, 121.38, 114.70, 107.64, 96.59 (d, $J_{\text{C-F}}$ = 108.8 Hz), 62.76, 56.32, 55.94; MS (CI, NH_3) m/z : 237 $[\text{M} + \text{H}]^+$, 254 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{13}\text{H}_{14}\text{FO}_3$: $[\text{M} + \text{H}]^+$ 237.0927, found 237.0933.

7-Fluoro-5,8-dimethoxynaphthalen-1-yl acetate (290)



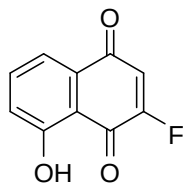
Acetic anhydride (1.13 mL, 12.0 mmol) was added to a solution of naphthol **222** (2.33g, 10.0 mmol) and DMAP (202 mg, 2.0 mmol) in pyridine (5 mL) and dichloromethane (15 mL) and the resulting mixture stirred at room temperature for 15 hours. After this time, water (20 mL) was added. The organic phase was washed with 2 M hydrochloric acid (3 x 100 mL), water (50 mL), brine (50 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue chromatographed (dichloromethane) to yield the title product as a white crystalline solid (2.30g, 87%); mp 100-101 °C (ethanol); R_f : 0.40 (dichloromethane); IR: $\nu_{\max}$ 2944, 1763, 1610, 1587, 1365, 1211, 1046, 985, 761; ^1H NMR (400 MHz, CDCl_3) δ 8.16 (d, $J = 7.6$ Hz, 1H, Ar-*H*4), 7.42 (t, $J = 7.6$ Hz, 1H, Ar-*H*3), 7.19 (d, $J = 7.6$ Hz, 1H, Ar-*H*2), 6.70 (d, $J_{\text{H-F}} = 12.4$ Hz, 1H, Ar-*H*6), 3.98 (s, 3H, Ar- OCH_3), 3.94 (s, 3H, Ar- OCH_3), 2.42 (s, 3H, $\text{CH}_3\text{CO-Ar}$); ^{13}C NMR (100 MHz, CDCl_3) δ 169.98, 154.51, 153.57 (d, $J_{\text{C-F}} = 189$ Hz), 152.30 (d, $J_{\text{C-F}} = 42.0$ Hz), 145.79 (d, $J_{\text{C-F}} = 68$ Hz), 145.76, 134.27, 134.13, 124.93, 124.30, 122.52, 121.43, 120.79, 96.65 (d, $J_{\text{C-F}} = 26.9$ Hz), 62.48, 55.98, 20.73; MS (CI, NH_3) m/z : 282 $[\text{M}+\text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{14}\text{H}_{17}\text{FNO}_4$ $[\text{M} + \text{NH}_4]^+$: 282.1142, found 282.1149; Elem. Anal. calc. for $\text{C}_{14}\text{H}_{13}\text{FO}_4$: C 63.63%, H 4.96%, found: C 63.72%, H 5.01%.

7-Fluoro-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate (291)



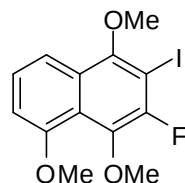
A solution of **290** (3.43 g, 13.0 mmol) in acetonitrile (260 mL) was added slowly to an aqueous solution of ceric ammonium nitrate (17.82 g, 32.5 mmol in 52 mL) at 0 °C and warmed to room temperature over the course of 30 minutes, after which time the solution was diluted with dichloromethane (200 mL). The organic phase was separated, washed with brine (200 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (dichloromethane) to yield the title product as a yellow crystalline solid (2.31 g, 76%); R_f : 0.36 (dichloromethane); mp 118-119 °C (ethanol); IR: $\nu_{\max}$ 1776, 1765, 1663, 1647, 1588, 1175, 1140, 986, 871, 715; ^1H NMR (400 MHz, CDCl_3) δ 8.09 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.4$ Hz, 1H, Ar-*H*), 7.84 (t, $J = 7.8$ Hz, 1H, Ar-*H*), 7.45 (dd, $J_1 = 8.0$ Hz, $J_2 = 0.8$ Hz, 1H, Ar-*H*), 6.66 (d, $J_{\text{H-F}} = 10.0$ Hz, 1H, CF=C-*H*), 2.48 (s, 3H, $\text{CH}_3\text{CO-}$); ^{13}C NMR (100 MHz, CDCl_3) δ 183.70 (d, $J_{\text{C-F}} = 61.6$ Hz), 176.30 (d, $J_{\text{C-F}} = 99.6$ Hz), 169.28, 162.68, 159.80, 150.10, 135.88, 133.45, 130.05, 125.13, 121.98, 116.40 (d, $J_{\text{C-F}} = 38.8$ Hz), 21.02; MS (CI, NH_3) m/z : 252 $[\text{M}+\text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{12}\text{H}_{11}\text{FNO}_4$ $[\text{M} + \text{NH}_4]^+$: 252.0672 found 252.0674; Elem. Anal. calc. for $\text{C}_{12}\text{H}_7\text{FO}_4$: C 61.55%, H 3.01%, found: C 61.63%, H 2.87%.

2-Fluoro-8-hydroxynaphthalene-1,4-dione (289)



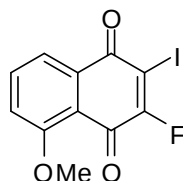
Anhydrous aluminium trichloride (2.13 g, 16 mmol) was added portionwise to a solution of **291** (375 mg, 1.6 mmol) in dichloromethane (20 mL), turning the reaction mixture intensely purple. After stirring at room temperature for 1 hour, the solution was quenched with water (10 mL), followed by dilute hydrochloric acid (10 mL). The organic layer was separated, washed with dilute acid, dried over magnesium sulfate, concentrated under reduced pressure, and the resulting residue was chromatographed (4:1 hexanes/ethyl acetate) to deliver the title compound as an orange crystalline solid (223mg, 73%); R_f : 4:1 (ethyl acetate/hexanes); mp 151-153 °C (methanol); IR: $\nu_{\max}$ 3067, 1776, 1765, 1678, 1646, 1588, 1165, 1140, 870; ^1H NMR (400 MHz, CDCl_3) δ 11.49 (s, 1H, Ar-OH), 7.72-7.65 (m, 2H, Ar-H6 and Ar-H5), 7.32 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.6$ Hz, 1H, Ar-H7), 6.66 (d, $J_{\text{H-F}} = 10.4$ Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3) δ 183.61 (d, $J_{\text{C-F}} = 56.8$ Hz), 182.51 (d, $J_{\text{C-F}} = 96.4$ Hz), 162.66, 160.90 (d, $J_{\text{C-F}} = 225$ Hz), 137.56, 131.72, 124.81, 119.64, 118.14 (d, $J_{\text{C-F}} = 34.0$ Hz), 113.86 (d, $J_{\text{C-F}} = 34.0$ Hz); MS (CI, NH_3) m/z : 209 $[\text{M-H}+\text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{10}\text{H}_6\text{FO}_3$ $[\text{M} + \text{H}]^+$: 193.0301, found: 193.0293; Elem. Anal. calc. for $\text{C}_{10}\text{H}_5\text{FO}_3$: C 62.51%, H 2.62%, found: C 62.57%, H 2.61%.

3-Fluoro-2-iodo-1,4,5-trimethoxynaphthalene (**293**)



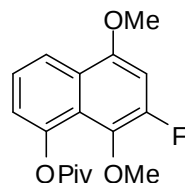
A solution of *n*-butyllithium (2.07 M in hexanes, 483 μ L, 1.0 mmol) was added dropwise to a solution of fluoride **292** (236 mg, 1.0 mmol) in THF (5 mL) at -78°C . After stirring at this temperature for 30 minutes, a solution of iodine (304 mg, 1.2 mmol) in THF (3 mL) was added and the solution was warmed to room temperature and stirred for a further 30 minutes, before being quenched with water (10 mL) and extracted with diethyl ether (2 x 10 mL). The organic phase was washed with brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (1:1 dichloromethane/hexanes) to yield the title product as a white, crystalline solid (304 mg, 84%); R_f : 0.45 (1:1 dichloromethane/hexanes); mp $79-80^{\circ}\text{C}$ (ethyl acetate/hexanes); IR: ν_{max} 2936, 1587, 1368, 1261, 1060, 1014, 747; ^1H NMR (400 MHz, CDCl_3) δ 7.66 (d, $J = 8.0$ Hz, 1H, Ar-*H*8), 7.37 (t, $J = 8.0$ Hz, 1H, Ar-*H*7), 6.91 (d, $J = 8.0$ Hz, 1H, Ar-*H*6), 4.00 (s, 3H, ArOCH₃), 3.94 (s, 3H, ArOCH₃), 3.93 (s, 3H, ArOCH₃); ^{13}C NMR (100 MHz, CDCl_3) δ 156.70 (d, $J_{\text{C-F}} = 26.8$ Hz), 153.47 (d, $J_{\text{C-F}} = 76.0$ Hz), 150.98, 139.68 (d, $J_{\text{C-F}} = 62.8$ Hz), 127.39, 126.19, 121.36, 114.92, 107.39, 79.63 (d, $J_{\text{C-F}} = 103.2$ Hz), 62.74, 61.71, 56.30; MS (CI, NH_3) m/z : 363 $[\text{M} + \text{H}]^+$, 380 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{13}\text{H}_{13}\text{FIO}_3$ $[\text{M} + \text{H}]^+$: 362.9893, found: 362.9900; Elem. Anal. calc. for $\text{C}_{12}\text{H}_7\text{FO}_4$: C 43.12%, H 3.34%, found: C 43.16%, H 3.29%.

3-Fluoro-2-iodo-5-methoxynaphthalene-1,4-dione (294)



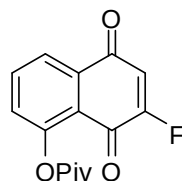
A solution of dimethoxynaphthalene **293** (362 mg, 1.0 mmol) in acetonitrile (40 mL) was added slowly to an aqueous solution of ceric ammonium nitrate (1.37 g, 2.5 mmol in 10 mL) at 0 °C and warmed to room temperature over the course of 30 minutes, after which time the solution was diluted with dichloromethane (20 mL). The organic phase was separated, washed with brine (20 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (dichloromethane) to yield the title product as an intensely yellow solid (282 mg, 85%); R_f : 0.38 (dichloromethane); mp 172-173 °C (ethyl acetate/hexanes); IR: $\nu_{\max}$ 2938, 2844, 1659, 1618, 1582, 1567, 1470, 1270, 1190, 1175, 1156, 1058, 978, 714; ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, J = 8.0 Hz, 1H, Ar-*H*8), 7.71 (t, J = 8.0 Hz, 1H, Ar-*H*7), 7.35 (d, J = 8.0 Hz, Ar-*H*6), 4.04 (s, 3H, ArOCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 179.53, 172.65 (d, $J_{\text{C-F}}$ = 100.0 Hz), 166.24, 163.41, 160.70, 135.85, 132.40, 120.99, 118.51, 97.94 (d, $J_{\text{C-F}}$ = 67.6 Hz), 56.64; MS (CI, NH_3) m/z : 333 $[\text{M}+\text{H}]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{11}\text{H}_7\text{FIO}_3$ $[\text{M}+\text{H}]^+$: 332.9424, found 332.9422; Elem. Anal. calc. for $\text{C}_{11}\text{H}_6\text{FIO}_3$: C 39.79%, H 1.82%, found: C 39.81%, H 1.89%.

7-Fluoro-5,8-dimethoxynaphthalen-1-yl pivalate (299)



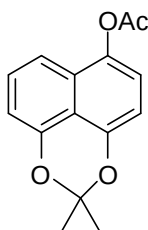
Pivaloyl chloride (985 μ L, 8.0 mmol) was added to a solution of naphthol **222** (222 mg, 1.0 mmol) and DMAP (202 mg, 2.0 mmol) in pyridine (0.5 mL) and dichloromethane (2 mL) and the resulting mixture was stirred at room temperature for 15 hours, before water was added. The organic phase was washed with 2 M hydrochloric acid (3 x 10 mL), water (5 mL), brine (5 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue chromatographed (8:1 hexanes/ethyl acetate) to yield the title product as a white crystalline solid (260 mg, 85%); mp 58-60 $^{\circ}$ C (ethanol); R_f : 0.40 (dichloromethane); IR: $\nu_{\max}$ 2975, 2941, 1748, 1608, 1589, 1367, 1345, 1240, 1078, 1041, 987; ^1H NMR (400 MHz, CDCl_3) δ 8.16 (d, $J_1 = 8.0$ Hz, 1H, Ar-*H*4), 7.42 (t, $J = 8.0$ Hz, 1H, Ar-*H*3), 7.07 (d, $J = 8.0$ Hz, 1H, Ar-*H*2), 6.67 (d, $J_{\text{H-F}} = 12.8$ Hz, 1H, Ar-*H*6), 3.96 (s, 3H, ArOCH_3), 3.88 (s, 3H, ArOCH_3), 1.45 (s, 9H, $\text{COC}(\text{CH}_3)_3$); ^{13}C NMR (100 MHz, CDCl_3) δ 177.44, 154.26, 152.34 (d, $J_{\text{C-F}} = 42.4$ Hz), 151.84, 146.67 (d, $J_{\text{C-F}} = 30.8$ Hz), 134.80 (d, $J_{\text{C-F}} = 50.0$ Hz), 124.61 (d, $J_{\text{C-F}} = 64.0$ Hz), 123.02, 121.29, 120.58, 96.65 (d, $J_{\text{C-F}} = 110.4$ Hz), 62.60 (d, $J_{\text{C-F}} = 19.6$ Hz), 55.97, 39.14, 27.38; MS (CI, NH_3) m/z : 324 $[\text{M}+\text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{17}\text{H}_{23}\text{FNO}_4$ $[\text{M} + \text{NH}_4]^+$; 324.1611, found: 324.1604; Elem. Anal. calc. for $\text{C}_{17}\text{H}_{19}\text{FO}_4$: C 66.65%, H 6.25%, found: C 66.64%, H 6.17%.

7-Fluoro-5,8-dioxo-5,8-dihydronaphthalen-1-yl pivalate (302)



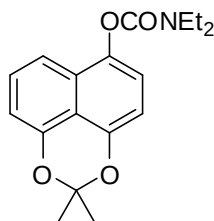
A solution of dimethoxynaphthalene **299** (3.43g, 13.0 mmol) in acetonitrile (100 mL) was added slowly to an aqueous solution of ceric ammonium nitrate (6.85 g, 12.5 mmol in 28 mL) at 0 °C, and warmed to room temperature over the course of 30 minutes after which time the solution was diluted with dichloromethane (100 mL). The organic phase was separated, washed with water (100 mL), brine (100 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (4:1 hexanes/ethyl acetate) to yield the title compound as a yellow powder (1.17 g, 85%); R_f : 0.58 (4:1 hexanes/ethyl acetate); mp 71-72 °C (ethanol); IR: $\nu_{\max}$ 2977, 1756, 1689, 1671, 1182; ^1H NMR (400 MHz, CDCl_3) δ 8.09 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz, 1H, Ar-*H*4), 7.82 (t, $J = 8.0$ Hz, 1H, Ar-*H*3), 7.39 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz, 1H, Ar-*H*2), 6.65 (d, $J_{\text{H-F}} = 10.0$ Hz, 1H, CF=CH); 1.48 (s, 9H, Ar-OC(CH₃)₃); ^{13}C NMR (100 MHz, CDCl_3) δ 183.83 (d, $J_{\text{C-F}} = 74.0$ Hz), 176.48, 176.15 (d, $J_{\text{C-F}} = 24.0$ Hz), 161.29 (d, $J_{\text{C-F}} = 294$ Hz), 150.68, 135.62, 133.46, 130.05, 124.98, 122.45 (d, $J_{\text{C-F}} = 24.0$ Hz), 116.23 (d, $J_{\text{C-F}} = 40.4$ Hz), 39.28, 27.17; MS (CI, NH_3) m/z : 294 $[\text{M}+\text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{15}\text{H}_{17}\text{FNO}_4$ $[\text{M} + \text{NH}_4]^+$: 294.1142, found 294.1136; Elem. Anal. calc. for $\text{C}_{15}\text{H}_{13}\text{FO}_4$: C 65.21%, H 4.74%, found: C 65.20%, H 4.78%.

2,2-Dimethylnaphtho[1,8-*de*][1,3]dioxin-6-yl acetate (**305**)



A suspension of juglone **301** (174 mg, 1.0 mmol) in diethyl ether (5 mL) was stirred vigorously with an aqueous solution of sodium dithionite (3.10 g, 17.5 mmol, in 10 mL) for 30 minutes. After this time, the organic layer was separated and dried over magnesium sulfate, and concentrated under reduced pressure to yield an off-white solid (176 mg). This solid was immediately dissolved in acetone (25 mL) and sulfuric acid (352 μ L) was slowly added to the resulting solution, which was stirred at room temperature for 18 hours, after which time the mixture was diluted with water (25 mL) and extracted into chloroform (4 x 20 mL). The combined organic phases were dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue (439 mg) and DMAP (20 mg, 0.2 mmol) were dissolved in pyridine (2 mL). Acetic anhydride (113 μ L) was added dropwise to this solution and the resulting mixture was stirred at room temperature for 18 hours. After this time, water (50 mL) was added slowly, the mixture was diluted with chloroform (3 x 50 mL), and the organic phase was separated, washed with brine (25 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (4:1 hexanes/ethyl acetate) to yield the title compound as an off-white crystalline solid (139 mg, 54% over three steps); mp 72-73 °C (ethyl acetate/hexanes); R_f : 0.36 (4:1 hexanes/ethyl acetate); IR: $\nu_{\max}$ 2971, 2947, 1751, 1520, 1214, 1188, 1037, 836; ^1H NMR (400 MHz, CDCl_3) δ 7.43 (t, J = 8.0 Hz, 1H, Ar-*H*8), 7.37 (d, J = 8.0 Hz, 1H, Ar-*H*7), 7.15 (d, J = 8.0 Hz, 1H, Ar-*H*5), 6.89 (d, J = 8.0 Hz, 1H, Ar-*H*9), 6.62 (d, J = 8.0 Hz, 1H, Ar-*H*4), 2.44 (s, 3H, COCH_3), 1.86 (s, 6H, $\text{C}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 169.69, 148.21, 145.77, 140.17, 127.99, 127.22, 119.46, 114.02, 113.93, 109.54, 108.16, 102.01, 25.02, 20.91; MS (CI, NH_3) m/z : 259 $[\text{M} + \text{H}]^+$, 276 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{15}\text{H}_{15}\text{O}_4$ $[\text{M} + \text{H}]^+$: 259.0970, found 259.0971.

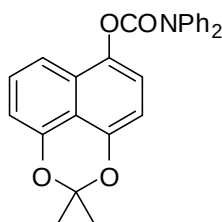
2,2-Dimethylnaphtho[1,8-*de*][1,3]dioxin-6-yl diethylcarbamate (309)



A suspension of juglone **301** (12.19 g, 70 mmol) in diethyl ether (350 mL) was stirred vigorously with an aqueous solution of sodium dithionite (97.5 g, 560 mmol, in 350 mL) for 30 minutes. After this time, the organic phase was separated and dried over magnesium sulfate, and concentrated under reduced pressure to yield an off-white solid (11.33 g). This solid was immediately dissolved in acetone (1 L) and sulfuric acid (13 mL) was slowly added to the resulting solution, which was stirred at room temperature for 18 hours, after which time the mixture was diluted with water (250 mL) and extracted into chloroform (4 x 250 mL). The combined organic phases were dried over magnesium sulfate, and concentrated under reduced pressure to yield a dark orange oil (22.87 g). A portion of this oil (10.81 g), as a solution in THF (25 mL), was added dropwise to a suspension of NaH (3.60 g, 90.0 mmol) in THF (25 mL). After five minutes, diethylcarbamoyl chloride (7.1 mL, 7.60 g, 60.0 mmol) was slowly added to the mixture, which was subsequently stirred at room temperature for 20 hours. After this time, water (50 mL) was added slowly, followed by saturated aqueous ammonium chloride (50 mL). The solution was then diluted with diethyl ether (100 mL), and the organic phase was separated, dried over magnesium sulfate, concentrated under reduced pressure and chromatographed (4:1 hexanes/ethyl acetate) to yield the title compound as an off-white crystalline solid (5.93 g, 18.8 mmol, 57% over three steps); R_f : 0.67 (4:1 hexanes/ethyl acetate); mp 56-58 °C (ethanol); IR: $\nu_{\max}$ 2975, 1722, 1608, 1411, 1268, 1155; ^1H NMR (400 MHz, CDCl_3) δ 7.45 (m, 2H, Ar-*H*), 7.22 (d, 1H, J = 8.4 Hz, Ar-*H*), 6.90 (m, 1H, Ar-*H*), 6.85 (d, 1H, J = 8.0 Hz, Ar-*H*); 3.61 (q, 2H, J = 6.8 Hz, - NCH_2 -), 3.46 (q, 2H, J = 6.8 Hz, - NCH_2 -), 1.68 (s, 6H, - $\text{C}(\text{CH}_3)_2$), 1.39 (t, 3H, J = 6.8 Hz, - NCH_2CH_3), 1.27 (t, 3H, J = 6.8 Hz, - NCH_2CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 154.48, 148.21, 145.26, 141.01, 128.00, 127.82, 119.65, 114.27, 113.96, 109.37, 108.34, 101.94, 42.40, 42.02, 25.23, 14.48, 13.47; MS (CI, NH_3) m/z : 316 $[\text{M}+\text{H}]^+$, 333 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc.

for $\text{C}_{18}\text{H}_{22}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 316.1549 $[\text{M} + \text{H}]^+$, found: 316.1549 $[\text{M} + \text{H}]^+$; Elem.
Anal. calc. for $\text{C}_{18}\text{H}_{21}\text{NO}_4$: C 68.55%, H 6.71%, N 4.44%, found: C 68.60%, H
6.71%, N 4.41%.

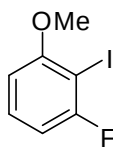
2,2-Dimethylnaphtho[1,8-*de*][1,3]dioxin-6-yl diphenylcarbamate (**310**)



A suspension of juglone **301** (12.19 g, 70 mmol) in diethyl ether (350 mL) was stirred vigorously with an aqueous solution of sodium dithionite (97.5 g, 560 mmol, in 350 mL) for 30 minutes. After this time, the organic phase was separated and dried over magnesium sulfate, and concentrated under reduced pressure to yield an off-white solid (11.33 g). This solid was immediately dissolved in acetone (1 L) and sulfuric acid (13 mL) was slowly added to the resulting solution, which was stirred at room temperature for 18 hours, after which time the mixture was diluted with water (250 mL) and extracted into chloroform (4 x 250 mL). The combined organic phases were dried over magnesium sulfate, and concentrated under reduced pressure to yield a dark orange oil (22.87 g). A portion of this oil (648 mg), as a solution in THF (4 mL), was added dropwise to a suspension of NaH (216 mg, 5.4 mmol) in THF (4 mL). After five minutes, diphenylcarbamoyl chloride (834 mg, 3.6 mmol) was slowly added to the mixture, which was subsequently stirred at room temperature for 20 hours. After this time, water (5 mL) was added slowly, followed by saturated aqueous ammonium chloride (5 mL). The solution was then diluted with diethyl ether (10 mL), and the organic phase was separated, dried over magnesium sulfate, concentrated under reduced pressure and chromatographed (4:1 hexanes/ethyl acetate) to yield the title compound as an off-white crystalline solid compound (403 mg, 49% over three steps); R_f : 0.46 (4:1 hexanes/ethyl acetate); mp 107-109 °C (hexanes/ethyl acetate); IR: $\nu_{\max}$ 2940, 1728, 1607, 1591, 1491, 1334, 1263, 1195, 1042, 1012, 872, 758, 675; ^1H NMR (400 MHz, CDCl_3) δ 7.49-7.28 (m, 13H, Ar-*H*), 7.22 (d, 1H, J = 8.4 Hz, Ar-*H*), 6.87 (d, 1H, J = 7.5 Hz, Ar-*H*), 6.83 (d, 1H, J = 8.2 Hz, Ar-*H*), 1.66 (s, 6H, -C(CH_3)₂); ^{13}C NMR (100 MHz, CDCl_3) δ 153.15, 148.12, 145.47, 141.01, 142.28, 140.66, 129.16, 127.90, 127.53, 126.66, 126.75, 126.64, 126.75, 119.633, 114.22, 109.45, 108.19, 101.99, 25.18; MS (CI, NH_3) m/z : 429 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{26}\text{H}_{22}\text{NO}_4$: 412.1549 $[\text{M} + \text{H}]^+$, found: 412.1553 $[\text{M} + \text{H}]^+$; Elem. Anal.

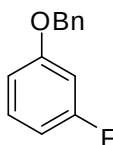
calc. for $\text{C}_{26}\text{H}_{21}\text{NO}_4$: C 75.90%, H 5.14%, N 3.40%, found: C 75.85%, H 5.16%, N 3.39%.

3-Fluoro-2-iodo-methoxybenzene (503)¹⁷⁶



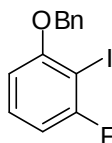
A solution of *n*-butyllithium (1.6 M in hexane, 6.9 mL, 11.0 mmol) was added dropwise to a solution of **218** (1.26 g, 10.0 mmol) in THF (20 mL) at -78°C . After stirring at this temperature for 90 minutes, a solution of iodine (3.81 g, 15.0 mmol) in THF (5 mL) was added and the resulting solution was allowed to warm to room temperature over 15 hours. After this time, water (10 mL) was added and the solution was extracted with diethyl ether (2 x 15 mL). The organic phase was washed with aqueous sodium thiosulfate (20 mL), brine (20 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue chromatographed (8:1 hexanes/ethyl acetate) to yield the title compound as a pale yellow oil (1.87 g, 74%); R_f (4:1 hexanes/ethyl acetate) 0.62; ^1H NMR (400 MHz, CDCl_3) δ 7.29 (m, 1H, Ar-*H*), 6.64 (t, 1H, $J = 8.31$ Hz, Ar-*H*), 3.93 (s, 3H, Ar- OCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 162.92 (d, $J_{\text{C-F}} = 221$ Hz), 161.60, 159.87 (d, $J_{\text{C-F}} = 6.4$ Hz), 130.20 (d, $J_{\text{C-F}} = 10.1$ Hz), 108.30 (d, $J_{\text{C-F}} = 24.3$ Hz), 106.43, 56.77; MS (CI, NH_3) m/z : 252 $[\text{M}]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_7\text{H}_6\text{FIO}$ $[\text{M}]^+$: 251.9447, found: 251.9448.

3-Fluorobenzyloxybenzene (338)¹⁷⁷



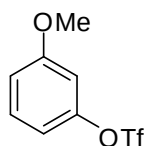
A solution of **245** (5.61 g, 50.0 mmol) in DMF (20 mL) was added slowly to a suspension of sodium hydride (60% dispersion in mineral oil, 3.00 g, 75.0 mmol) in DMF (80 mL) at 0 °C. After ten minutes, benzyl bromide (10.1 mL, 85.0 mmol) was slowly added to the resulting mixture, which was subsequently warmed to room temperature and stirred for 16 hours. After this time, water (50 mL) was added, and the mixture extracted into diethyl ether (2 x 75 mL). The organic phase was washed with brine (75 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (100:1 hexanes/ethyl acetate) to yield the title compound as a colourless oil (9.03 g, 89%); R_f : 0.44 (4:1 hexanes/ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 7.47-7.35 (m, 1H, Ar-*H*), 7.28-7.23 (m, 1H, Ar-*H*), 6.81-6.68 (m, 5H, -OCH₂Ar-*H*), 5.08 (s, 2H, OCH₂Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 163.6 (d, $J_{\text{C-F}}$ = 243 Hz), 160.20, 136.50, 130.29, 128.67, 128.16, 127.50, 107.74 (d, $J_{\text{C-F}}$ = 21.0 Hz), 102.6 (d, $J_{\text{C-F}}$ = 24.0 Hz), 70.26; MS (CI, NH_3) m/z : 202 $[\text{M}]^+$ 220 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{13}\text{H}_{15}\text{FNO}$ $[\text{M} + \text{NH}_4]^+$: 220.1138, found: 220.1140.

3-Fluoro-2-iodo-benzyloxybenzene (339)



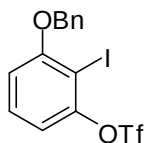
A solution of *n*-butyllithium (1.6 M in hexanes, 2.1 mL, 3.3 mmol) was added dropwise to a solution of **338** (607 mg, 3.0 mmol) in THF (6 mL) at -78°C . After stirring at this temperature for 90 minutes, a solution of iodine (1.91 g, 7.5 mmol) in THF (3 mL) was added and the resulting solution was warmed to room temperature over 2 hours. After this time, water (10 mL) was added and the solution was extracted with diethyl ether (2 x 15 mL). The organic phase was washed with aqueous sodium thiosulfate (20 mL), brine (20 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue chromatographed (9:1 hexanes/ethyl acetate) to yield the title compound as a colourless oil (1.22 g, 74%); R_f : 0.55 (4:1 hexanes/ethyl acetate); IR: ν_{max} 2987, 2901, 1590, 1450, 1238, 1056, 1027, 764, 731, 695; ^1H NMR (400 MHz, CDCl_3) δ 7.52 (d, $J = 7.4$ Hz, 2H, Ar-*H*), 7.43 (t, $J = 7.2$ Hz, $J = 7.7$ Hz, 2H, Ar-*H*), 7.36 (m, 1H, Ar-*H*), 7.28-7.23 (d, $J = 7.3$ Hz, 1H, Ar-*H*), 6.75 (t, 1H, $J = 8.0$ Hz, Ar-*H*), 6.67 (d, 1H, $J = 8.0$ Hz, Ar-*H*), 5.20 (s, 2H, OCH_2Ar); ^{13}C NMR (100 MHz, CDCl_3) 136.19, 130.14 (d, $J_{\text{C-F}} = 38.4$ Hz), 128.62, 128.03, 126.98, 108.55 (d, $J_{\text{C-F}} = 96.0$ Hz), 108.07, 71.23; MS (CI, NH_3) m/z : 345 [$\text{M} + \text{NH}_4$] $^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{13}\text{H}_{11}\text{FIO}$ [$\text{M} + \text{H}$] $^+$: 346.0104, found: 346.0107; Elem. Anal. calc. for $\text{C}_{13}\text{H}_{10}\text{FIO}$: C 47.59 %, H 3.07%, found: C 47.63%, H 3.62%.

3-Methoxyphenyl trifluoromethanesulfonate (**341**)¹⁷⁸



Trifluoromethanesulfonic anhydride (8.3 mL, 14.11 g, 50.0 mmol) was added dropwise to a solution of **304** (3.10 g, 25.0 mmol) and *N,N*-diisopropylethylamine (8.7 mL, 6.46 g, 50.0 mmol) in dichloromethane (36 mL) at -78°C . The solution was stirred at -78°C for 1 hour and then allowed to warm to room temperature over 2 hours. After this time, a saturated aqueous solution of ammonium chloride was added cautiously (30 mL), before the mixture was extracted into diethyl ether (2 x 50 mL). The organic phase was washed with brine (50 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (8:1 hexanes/ethyl acetate) to yield the title compound as a very pale yellow oil (2.18 g, 85%); R_f : 0.58 (4:1 hexanes/ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 7.34 (t, 1H, $J = 8.4$ Hz, Ar-*H*5), 6.93 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.2$ Hz, Ar-*H*4/*H*6), 6.87 (dd, 1H, $J = 8.4$ Hz, $J = 2.2$ Hz, Ar-*H*4/*H*6), 6.80 (t, 1H, $J = 2.4$ Hz, Ar-*H*2), 3.83 (s, 3H, Ar- OCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 160.87, 150.24, 130.54, 114.13, 113.23, 107.49, 55.70; MS (CI, NH_3) m/z : 256 $[\text{M}]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_8\text{H}_{11}\text{F}_3\text{NO}_4\text{S}$ $[\text{M} + \text{NH}_4]^+$: 274.0361, found: 274.0374.

3-(Benzyloxy)-2-iodophenyl trifluoromethanesulfonate (**334**)¹³³

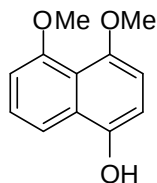


N,N-Di-*iso*-propylethylamine (23.0 mL, 17.09 g, 132 mmol) was added slowly to a solution of 2-iodoresorcinol (13.0 g, 55.1 mmol) in dichloromethane (130 mL) at -78°C . Subsequently, triflic anhydride (20.4 mL, 121 mmol) was added over 15 minutes *via* dropping funnel at -78°C . The resulting solution was stirred at this temperature for a further 15 minutes, before being warmed to 0°C , at which temperature the solution was stirred for a further 1 hour. After this time, the solution was quenched with slow addition of water (100 mL), dilution with dichloromethane (50 mL) and the organic phase was separated, washed with saturated aqueous sodium hydrogen carbonate solution (100 mL), brine (100 mL), dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue was dissolved in diethyl ether (55 mL) and hexanes (55 mL) and silica gel (13.5 g) was added. The mixture was stirred for 30 minutes, filtered, the filter cake washed with diethyl ether/hexanes (1:1, 180 mL), and the combined filtrate was concentrated under reduced pressure to yield **67** as a dark brown oil (24.28 g).

Caesium carbonate (18.98 g, 58.3 mmol) was added to a solution of crude **67** in 2-dimethoxyethane (100 mL) and the resulting suspension heated at 80°C for 5 hours, before being cooled to room temperature, whereupon benzyl bromide (6.93 mL, 9.96 g, 58.3 mmol) was added and the solution stirred at this temperature for a further 15 hours. After this time, diethylamine (2.5 mL, 1.78 g, 24.4 mmol) was added, and the solution stirred for 1 hour. After this time, 1 M hydrochloric acid (50 mL) was added slowly at 0°C , and the solution extracted into ethyl acetate (150 mL). The organic phase was washed with aqueous sodium hydrogen carbonate (100 mL), brine (100 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue chromatographed (20:1 hexanes/ethyl acetate) to yield the title compound as a white crystalline solid (21.52 g, 85%); R_f : 0.65 (4:1 hexanes/ethyl acetate); mp $86-87^{\circ}\text{C}$ (methanol), lit.¹³³ $86-87^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ

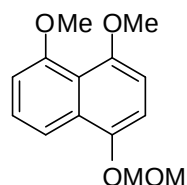
7.52 (d, $J = 7.4$ Hz, 2H, Ar-*H*), 7.45 (t, $J_1 = 7.0$ Hz, $J_2 = 7.7$ Hz, 2H, Ar-*H*), 7.38 (t, $J_1 = 8.2$ Hz, $J_2 = 8.4$ Hz, 2H, Ar-*H*), 7.00 (d, $J = 8.2$ Hz, 1H, Ar-*H*), 6.88 (d, $J = 8.3$ Hz, 1H, Ar-*H*), 5.22 (s, 2H, PhCH₂O-); ¹³C NMR (100 MHz, CDCl₃) δ 159.45, 151.36, 135.68, 130.35, 130.35, 128.73, 128.25, 127.04, 120.36, 117.18, 114.45, 111.69; MS (CI, NH₃) m/z : 476 [M + NH₄]⁺; HRMS (CI, NH₃) m/z calc. for C₁₄H₁₄F₃INO₄S [M + NH₄]⁺: 475.9640, found: 475.9647.

4,5-Dimethoxynaphthalen-1-ol (335)¹⁷⁹



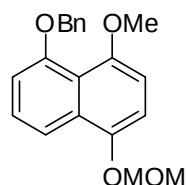
A solution of *n*-butyllithium (1.97 mL, 1.6 M in hexane) was added dropwise to a solution of **341** (338 μ L, 378 mg, 3.0 mmol) in THF (6 mL) at -78 °C. The solution was stirred at this temperature for 90 minutes, after which time 2-methoxyfuran (1.11 mL, 1.19 g, 12.0 mmol) was added, and the solution allowed to warm to room temperature over 16 hours. Saturated aqueous ammonium chloride (10 mL) was added, and the mixture was extracted with diethyl ether (2 x 10 mL). The organic phase was washed with brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was recrystallised from chloroform to yield the title compound as an off-white, crystalline solid (257 mg, 42%); mp 161-162 °C (chloroform), lit: 164 °C; R_f : 0.58 (4:1 hexanes/ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 8.47 (s, 1H, Ar-OH), 7.82 (d, 1H, J = 7.8 Hz, Ar-*H*), 7.37 (t, 1H, J = 8.3 Hz, Ar-*H*), 6.95 (d, 1H, J = 7.7 Hz, Ar-*H*), 6.83 (d, 1H, J = 8.3 Hz, Ar-*H*), 6.77 (d, 1H, J = 8.3 Hz, Ar-*H*), 3.91 (s, 3H, Ar- OCH_3), 3.82 (s, 3H, Ar- OCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 157.06, 150.51, 146.92, 128.13, 125.26, 118.99, 114.69, 108.41, 108.14, 106.80, 57.01, 55.62; MS (CI, NH_3) m/z : 205 $[\text{M}+\text{H}]^+$, 222 $[\text{M} + \text{NH}_4]^+$; HRMS (ESI) m/z calc. for $\text{C}_{12}\text{H}_{13}\text{O}_3$ $[\text{M} + \text{H}]^+$: 205.0865, found: 205.0864.

4,5-Dimethoxy-1-methoxymethoxynaphthalene (342)



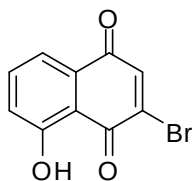
A solution of **335** (204 mg, 1.0 mmol) in DMF (1 mL) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil, 60 mg, 1.5 mmol) in DMF (6 mL), ensuring gas evolution was kept to a moderate level. On completion, methyl chloromethyl ether (152 μ L, 2.0 mmol) was added slowly, and the resulting mixture was stirred at room temperature for 3 hours. After this time, the mixture was quenched with water (10 mL) and extracted into diethyl ether (2 x 10 mL). The organic phase was washed with brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (2:1 hexanes/ethyl acetate) to deliver the title compound as a white crystalline solid (137 mg, 55%); R_f : 0.41 (4:1 hexanes/ethyl acetate); mp 51-52 $^{\circ}$ C (hexanes/ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 7.88 (d, 1H, J = 8.4 Hz, Ar- H), 7.42 (t, 1H, J = 8.4 Hz, Ar- H), 7.07 (d, 1H, J = 8.4 Hz, Ar- H), 6.93 (d, 1H, J = 7.7 Hz, Ar- H), 6.79 (d, 1H, J = 8.4 Hz, Ar- H), 5.33 (s, 2H, OCH_2O), 4.00 (s, 3H, Ar- OCH_3), 3.95 (s, 3H, Ar- OCH_3), 3.57 (s, 3H, $-\text{OCH}_2\text{OCH}_3$); ^{13}C NMR (100 MHz, CDCl_3) δ 156.94, 151.95, 146.95, 129.41, 126.11, 118.45, 114.60, 109.27, 106.97, 106.60, 95.44, 57.24, 56.52, 56.17; MS (CI, NH_3) m/z : 249 $[\text{M}+\text{H}]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{14}\text{H}_{17}\text{O}_4$ $[\text{M} + \text{H}]^+$: 249.1127, found: 249.1128; Elem. Anal. calc. for $\text{C}_{14}\text{H}_{16}\text{O}_4$: C 67.73%, H 6.50%, found: C 67.68%, H 6.47%.

5-Benzyloxy-4-methoxy-1-methoxymethoxynaphthalene (343)



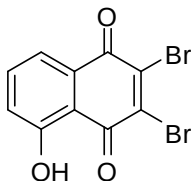
A solution of *n*-butyllithium (1.97 mL, 1.6 M in hexane) was added dropwise to a solution of **334** (1.37 g, 3.0 mmol) and 2-methoxyfuran (1.11 mL, 1.19 g, 12.0 mmol) in THF (6 mL), at -78°C . The solution was stirred at this temperature for 30 minutes, after which time it was allowed to warm to room temperature, before di-*iso*-propylethylamine (784 μL , 4.5 mmol) and then methyl chloromethyl ether (684 μL , 9.0 mmol) were added and the resulting mixture was stirred for a further 14 hours. After this time, the mixture was quenched with water (10 mL) and extracted into diethyl ether (2 x 10 mL). The organic phase was washed with brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (4:1 hexanes/ethyl acetate) to deliver the title compound as an off-white amorphous solid (408 mg, 42%); R_f : 0.52 (4:1 hexanes/ethyl acetate); IR: ν_{max} 2898, 2837, 1595, 1362, 1278, 1036, 801, 748; ^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, J = 8.6 Hz, 1H, Ar-*H*), 7.61 (d, J = 7.2 Hz, 2H, Ar-*H*), 7.51-7.31 (m, 4H, Ar-*H*), 7.06 (d, J = 8.6 Hz, 1H, Ar-*H*), 7.00 (d, J = 7.6 Hz, 1H, Ar-*H*), 6.78 (d, J = 8.6 Hz, 1H, Ar-*H*), 5.32 (s, 2H, OCH_2O), 5.22 (s, 2H, ArOCH_2Ph), 3.91 (s, 3H, Ar-OCH_3), 3.56 (s, 3H, $-\text{OCH}_2\text{OCH}_3$); ^{13}C NMR (100 MHz, CDCl_3) δ 155.92, 152.02, 146.87, 137.58, 129.48, 128.33, 127.50, 127.04, 126.04, 118.99, 115.11, 109.48, 109.25, 106.52, 95.44, 71.62, 57.00, 56.15; MS (CI, NH_3) m/z : 325 $[\text{M} + \text{H}]^+$; HRMS (ESI) m/z calc. for $\text{C}_{20}\text{H}_{21}\text{O}_4$ $[\text{M} + \text{H}]^+$: 325.1440, found: 325.1449.

2-Bromo-8-hydroxynaphthalene-1,4-dione (**347**)¹⁴⁶



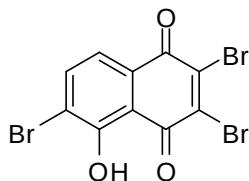
Bromine (4.03 mL, 78.8 mmol) was added to a solution of **301** (13.06 g, 75.0 mmol) in acetic acid (75 mL), and the dark orange solution was stirred at room temperature for 20 minutes. After this time, ice (approx. 175 g) was added and the solution was stirred for a further 15 minutes. The resulting yellow precipitate was isolated by filtration and immediately heated under reflux in ethanol (55 mL) for 30 minutes. The solution was cooled and the precipitate isolated by filtration and recrystallised from dichloromethane/ethanol to give the title compound as orange crystals (15.62 g, 82%), typically containing *ca.* 5% of the 2-bromojuglone isomer (inconsequential for next step); R_f : 0.67 (4:1 hexanes/ethyl acetate); mp 171-172 °C (ethanol), lit.¹⁴⁶ 172 °C; 3058, 1675, 1634, 1454, 1198, 1091, 745; ¹H NMR (400 MHz, CDCl₃) δ 11.76 (s, 1H, Ar-OH), 7.72-7.65 (m, 2H, Ar-H5 and Ar-H6), 7.52 (s, 1H, -CBr=CH-), 7.34 (dd, $J_1 = 7.9$ Hz, $J_2 = 1.48$ Hz, 1H, Ar-H7); ¹³C NMR (100 MHz, CDCl₃) δ 182.92, 181.66, 162.10, 141.23, 139.34, 137.23, 131.67, 124.77, 119.94, 113.97; MS (CI, NH₃) m/z : 271 [M + NH₄]⁺; HRMS (CI, NH₃) m/z calc. for C₁₀H₉⁷⁹BrNO₃ [M + NH₄]⁺: 268.9688, found: 268.9696; Elem. Anal. calc. for C₁₀H₅BrO₃: C 47.46%, H 1.99%, found: C 47.39%, H 2.06%.

2,3-Dibromo-5-hydroxynaphthalene-1,4-dione (348)¹⁴⁶



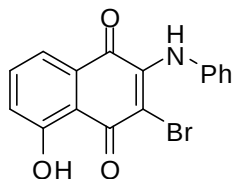
To a suspension of **347** (187 mg, 0.5 mmol) in ethanol (5 mL), 1.5 M sulfuric acid (1.65 mL, 2.48 mmol) was added, and the mixture heated at 100 °C for 2 hours. After this time, the solution was cooled and the precipitate formed was isolated by filtration and recrystallised from ethanol to give the title compound as an orange, crystalline solid (117 mg, 70%); R_f : 0.60 (4:1 hexanes/ethyl acetate); mp 168-169 °C (ethanol), lit.¹⁴⁶ 169 °C; IR: $\nu_{\max}$ 3101, 1671, 1639, 1553, 1452, 1200, 1125, 828, 714; ^1H NMR (400 MHz, CDCl_3) δ 11.72 (s, 1H, Ar-OH), 7.79 (dd, $J_1 = 7.3$ Hz, $J_2 = 0.6$ Hz, 1H, Ar-H8), 7.70 (t, $J = 8.0$ Hz, 1H, Ar-H7), 7.36 (dd, $J_1 = 8.3$ Hz, $J_2 = 0.6$ Hz, 1H, Ar-H6); ^{13}C NMR (100 MHz, CDCl_3) δ 180.79, 175.20, 167.57, 162.36, 143.48, 141.77, 137.02, 125.23, 121.65, 113.72; MS (CI, NH_3) m/z : 349 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{10}\text{H}_8^{79}\text{Br}_2\text{NO}_3$ $[\text{M} + \text{NH}_4]^+$: 346.8793, found: 346.8798; Elem. Anal. calc. for $\text{C}_{10}\text{H}_4\text{Br}_2\text{O}_3$: C 36.18%, H 1.21%, found: C 36.09%, H 1.19%.

2,3,6-Tribromo-5-hydroxynaphthalene-1,4-dione (356)¹⁵⁰



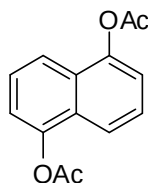
Bromine (39 μ L, 120 mg, 0.8 mmol) was added to a solution of **347** (127 mg, 0.5 mmol) in acetic acid (1 mL) and the resulting solution heated for 3 hours at 90 °C. On cooling, a precipitate formed, which was isolated by filtration and recrystallised from ethanol to yield the title compound as orange-red crystals (141 mg, 80%); R_f : 0.71 (4:1 hexanes/ethyl acetate); mp 172 °C (ethanol), lit.¹⁵⁰ 172 °C; IR: $\nu_{\max}$ 3064, 1668, 1641, 1414, 1253, 1195, 1121, 715; ^1H NMR (400 MHz, CDCl_3) δ 12.36 (s, 1H, Ar-OH), 7.98 (d, J = 8.1 Hz, 1H, Ar-*H*8), 7.66 (d, J = 8.1 Hz, 1H, Ar-*H*7); ^{13}C NMR (100 MHz, CDCl_3) δ 180.90, 174.69, 158.79, 143.92, 141.17, 140.20, 129.55, 121.79, 120.45, 114.08; MS (CI, NH_3) m/z : 427 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{10}\text{H}_7^{79}\text{Br}_3\text{NO}_3$ $[\text{M} + \text{NH}_4]^+$: 424.7898, found: 424.7896; Elem. Anal. calc. for $\text{C}_{10}\text{H}_3\text{Br}_3\text{O}_3$: C 29.23%, H 0.74%, found: C 29.27%, H 0.75%.

3-Bromo-5-hydroxy-2-(phenylamino)naphthalene-1,4-dione (352)¹⁴⁶



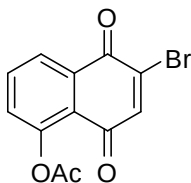
Aniline (54 μ L, 56 mg, 0.6 mmol) was added to a solution of **348** (166 mg, 0.5 mmol) in ethanol (13 mL), and the mixture was heated under reflux for 20 minutes, during which time the solution developed an intense purple colour. After this time, the solution was cooled and the resulting precipitate was isolated by filtration and recrystallised from acetone to give the title compound as a purple crystalline solid (142 mg, 83%); R_f : 0.55 (4:1 hexanes/ethyl acetate); mp 213-215 $^{\circ}$ C (acetone), lit.¹⁴⁶ 215 $^{\circ}$ C; IR: $\nu_{\max}$ 3234, 2988, 1676, 1620, 1586, 1556, 1462, 1446, 1278, 1228, 690; ^1H NMR (400 MHz, CDCl_3) δ 12.54 (s, 1H, Ar-OH), 7.94 (s, 1H, Ph-NH-), 7.71 (d, J = 7.7 Hz, 1H, Ar-H8), 7.58 (t, J = 7.3 Hz, 1H, Ar-H7), 7.40 (t, J = 7.3 Hz, 2H, Ar-H), 7.33 (d, J = 7.3 Hz, 2H, Ar-H), 7.15 (d, J = 7.3 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3) δ 183.11, 179.33, 161.29, 144.73, 136.93, 129.77, 128.58, 126.35, 126.16, 125.40, 125.19, 124.74, 120.24, 114.16, 108.24, 106.53, 90.96; MS (CI, NH_3) m/z : 344 $[\text{M}]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{16}\text{H}_{11}^{79}\text{BrNO}_3$ $[\text{M} + \text{H}]^+$; 343.922, found: 343.9908; Elem. Anal. calc. for $\text{C}_{16}\text{H}_{10}\text{BrNO}_3$: C 55.84%, H 2.93%, N 4.07%, found: C 55.75%, H 2.83%, N 3.98%.

Naphthalene-1,5-diyl acetate (358)¹⁸⁰



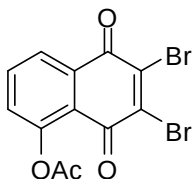
Pyridine (36 mL) was slowly added to naphthalene-1,5-diol (8.26 g, 50.0 mmol), and acetic anhydride (14.15 mL, 15.31 g, 150 mmol) was then added slowly to the resulting black solution, which was stirred at room temperature for 4 hours. After this time, water (100 mL) was added and the solution was extracted with ethyl acetate (2 x 100 mL). The organic phase was separated, washed with 1 M hydrochloric acid (3 x 100 mL) or aqueous copper (II) sulfate (3 x 100 mL), brine (100 mL), dried over magnesium sulfate, concentrated under reduced pressure and recrystallised from toluene to yield the title product as a white crystalline solid (11.19 g, 92%); R_f : 0.33 (4:1 hexanes/ethyl acetate); mp 156-158 °C (ethanol), lit.¹⁸⁰ 158-159 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.82 (d, J = 8.5 Hz, 2H, Ar-*H*4 and Ar-*H*8), 7.54 (t, J = 8.0 Hz, 2H, Ar-*H*3 and Ar-*H*7), 7.33 (d, J = 7.5 Hz, 2H, Ar-*H*2 and Ar-*H*6), 2.50 (s, 6H, COCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 169.37, 146.74, 128.17, 126.10, 119.34, 118.86, 21.06; MS (CI, NH_3) m/z : 262 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{14}\text{H}_{16}\text{NO}_4$ $[\text{M} + \text{NH}_4]^+$: 262.1079, found: 262.1087.

6-Bromo-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate (359)¹⁵¹



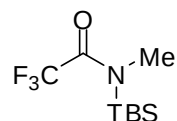
A warmed solution of **358** (10.99 g, 45.0 mmol) in acetic acid (300 mL) was added to a solution of NBS (31.88 g, 180 mmol) in water (600 mL) and acetic acid (300 mL), at 65 °C over 30 minutes. The resulting mixture was then heated at this temperature for a further 90 minutes before being added to water (600 mL) and this suspension was extracted with chloroform (4 x 500 mL), the combined organic phases were then washed with water (500 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was recrystallised from ethanol to yield the title product as yellow-orange crystals (11.28 g, 76%); R_f : 0.40 (4:1 hexanes/ethyl acetate); mp 154–156 °C (ethanol), lit.¹⁵¹ 154–156 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.16 (dd, $J_1 = 8.0$ Hz, $J_2 = 0.8$ Hz, 1H, Ar-*H*4), 7.79 (t, $J = 8.0$ Hz, 1H, Ar-*H*3), 7.44 (dd, $J_1 = 8.0$ Hz, $J_2 = 0.8$ Hz, 1H, Ar-*H*2), 7.41 (s, 1H, -CBr=CH-), 2.46 (s, 3H, COCH₃) ; ^{13}C NMR (100 MHz, CDCl_3) δ 180.94, 177.42, 169.31, 149.82, 141.42, 138.53, 134.98, 132.53, 130.34, 126.37, 123.08, 21.07; MS (CI, NH_3) m/z : 314 $[\text{M} + \text{NH}_4]^+$ (with ^{81}Br); HRMS (CI, NH_3) m/z calc. for $\text{C}_{12}\text{H}_7^{79}\text{BrNO}_4$ $[\text{M} + \text{NH}_4]^+$: 311.9871, found: 311.9878.

6,7-Dibromo-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate (360)¹⁴⁶



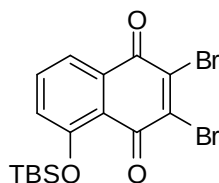
Bromine (113 μ L, 352 mg, 2.2 mmol) was added to a suspension of **359** (590 mg, 2 mmol) in acetic acid (8 mL) and heated to 55 $^{\circ}$ C. The resulting solution was stirred at this temperature for 3 hours. After this time, the suspension was cooled and ice (approx. 8 g) was added. The resulting mixture was stirred for a further 30 minutes, before the precipitate was isolated by filtration and recrystallised from ethanol to yield the title compound as an orange solid (85%); R_f : 0.35 (4:1 hexanes/ethyl acetate); mp 171-172 $^{\circ}$ C (ethanol), lit.¹⁴⁷ 172 $^{\circ}$ C; ^1H NMR (400 MHz, CDCl_3) δ 8.21 (d, J = 7.7 Hz, 1H, Ar-*H*4), 7.88 (t, J = 7.9 Hz, 1H, Ar-*H*3), 7.52 (d, J = 8.0 Hz, 1H, Ar-*H*2), 2.45 (s, 3H, COCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 182.65, 180.00, 169.01, 150.82, 136.00, 131.34, 129.40, 127.72, 122.66, 110.59, 58.80, 20.94; MS (CI, NH_3) m/z : 392 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{12}\text{H}_{10}^{79}\text{Br}_2\text{NO}_4$ $[\text{M} + \text{NH}_4]^+$: 389.8977, found: 389.8989.

***N*-(*tert*-Butyldimethylsilyl)-2,2,2-trifluoro-*N*-methylacetamide (372)¹⁵³**



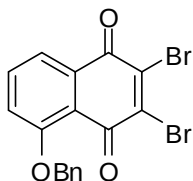
A solution of *N*-methyltrifluoroacetamide (6.36 g, 50.0 mmol) in acetonitrile (2 mL) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 1.97g, 49.0 mmol) in benzene (20 mL) and acetonitrile (20 mL) at 0 °C. When addition was complete, *tert*-butyldimethylchlorosilane (7.54 g, 57.5 mmol) was added portionwise to the mixture over 20 minutes, and the resulting mixture was stirred at 0 °C for 2 hours. After this time, the mixture was filtered, concentrated under reduced pressure and the residue was distilled to yield the title product as a colourless oil (4.83 g, 76%); bp 166-170 °C (760 mmHg) characterised only by ¹H NMR; ¹H NMR (400 MHz, CDCl₃): δ 0.26 (s, 6H, N-Si (CH₃)₂), 0.99 (s, 9H, SiC (CH₃)₃), 3.07 (s, 3H, NCH₃).

2,3-Dibromo-5-(*tert*-butyldimethylsilyloxy)naphthalene-1,4-dione (371)



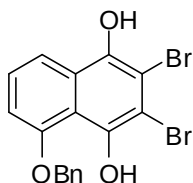
A solution of **372** (7.84 g, 32.5 mmol) and *tert*-butyldimethylchlorosilane (49 mg, 0.33 mmol) in acetonitrile (10 mL) was added dropwise to a solution of **348** (2.16 g, 6.5 mmol) in dry acetonitrile (55 mL). The resulting mixture was heated at 60 °C and stirred for 3 hours. After this time, the mixture was concentrated under reduced pressure and the residue was taken up in hexane, cooled to 0 °C for 3 hours and then filtered to remove the excess trifluoroacetamide. The filtrate was concentrated under reduced pressure and the residue was recrystallised to afford a dark orange crystalline solid (2.08 g, 72%); R_f : 0.74 (3 : 2 dichloromethane / hexanes); mp 95-97 °C; IR: $\nu_{\max}$ 1670, 1585, 1574, 1463, 1474, 1264, 1233, 1215, 750, 690 2933, 2857, 1673, 1640, 1588, 1569, 1554, 1438, 1262, 1216, 1171, 1166, 1133, 1097, 980, 836, 734; ^1H NMR (400 MHz, CDCl_3) δ 7.83 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.2$ Hz, 1H, Ar-*H*8), 7.58 (t, $J = 7.8$ Hz, 1H, Ar-*H*7), 7.20 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.2$ Hz, 1H, Ar-*H*6), 1.06 (s, 9H, $\text{OSiC}(\text{CH}_3)_3$), 0.29 (s, 6H, $\text{OSi}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 176.26, 173.89, 157.14, 144.88, 139.96, 134.79, 132.79, 128.27, 121.99, 120.74, 25.76, 18.51, -4.03; MS (CI, NH_3) m/z : 464 $[\text{M} + \text{NH}_4]^+$ (^{81}Br and ^{79}Br); HRMS (CI, NH_3) m/z calc. for $\text{C}_{16}\text{H}_{18}^{81}\text{Br}_2\text{O}_3\text{Si}$ $[\text{M} + \text{NH}_4]^+$: 444.9470, found: 444.9478; Elem. Anal. calc. for $\text{C}_{16}\text{H}_{18}\text{Br}_2\text{O}_3\text{Si}$: C 43.07%, H 4.07%, found: C 43.03%, H 4.00%.

5-Benzyloxy-2,3-dibromonaphthalene-1,4-dione (361)



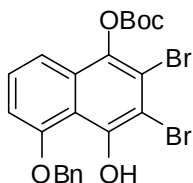
Benzyl bromide (2.38 mL, 3.42 g, 20.0 mmol) was added to a suspension of silver (I) oxide (4.64 g, 20.0 mmol) and **348** (1.66g, 5.0 mmol) in chloroform (15 mL) and the resulting mixture was stirred for 18 hours. After this time, the mixture was filtered through Celite (which was washed with further portions of chloroform), concentrated under reduced pressure and the resulting residue was chromatographed (3:2 dichloromethane/hexanes) to deliver the title compound as a yellow crystalline solid (1.71 g, 81%); R_f : 0.29 (2:1 dichloromethane/hexanes); mp 180-181 °C (ethanol); IR: $\nu_{\max}$ 1670, 1585, 1574, 1463, 1474, 1264, 1233, 1215, 750, 690; ^1H NMR (400 MHz, CDCl_3) δ 7.83 (dd, $J_1 = 7.7$ Hz, $J_2 = 0.8$ Hz, 1H, Ar-*H*8), 7.66 (t, $J = 8.0$ Hz, 1H, Ar-*H*7), 7.56 (d, $J = 7.5$ Hz, 2H, Ar-*H*6 and $\text{CH}_2\text{Ar-H}$), 7.44-7.32 (m, 4H, $\text{CH}_2\text{Ar-H}$), 5.31 (s, 2H, $\text{ArCH}_2\text{O-}$); ^{13}C NMR (100 MHz, CDCl_3) δ 176.20, 173.83, 159.50, 144.98, 139.73, 135.56, 135.37, 132.98, 128.81, 128.17, 126.80, 121.20, 119.98, 118.85, 71.14; MS (EI) m/z : 422 $[\text{M}]^+$ (^{81}Br and ^{79}Br), 91 $[\text{PhCH}_2]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{17}\text{H}_{10}^{79}\text{Br}_2\text{O}_3$ $[\text{M}]^+$: 419.8997, found: 419.8988; Elem. Anal. calc. for $\text{C}_{10}\text{H}_4\text{Br}_2\text{O}_3$: C 48.38%, H 2.39%, found: C 48.29%, H 2.32%.

5-Benzyloxy-2,3-dibromonaphthalene-1,4-diol (**362**)



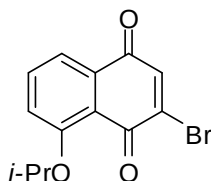
An aqueous solution of sodium dithionite (8.85 g, 50.0 mmol in 100 mL) was added to a solution of **361** (2.11 g, 5.0 mmol) in dichloromethane (100 mL) and the biphasic system was stirred vigorously for 30 minutes. After this time, the phases were separated and the aqueous phase was washed with dichloromethane (2 x 50 mL). The combined organic phases were washed with brine (100 mL), dried over magnesium sulfate and concentrated under reduced pressure to yield the title product as an off-white solid (1.99 g, 94%) which was generally used immediately as it is prone to aerial oxidation; ^1H NMR (400 MHz, CDCl_3) δ 9.90 (s, 1H, ArC4-OH), 7.85 (d, J = 8.8 Hz, 1H, Ar-*H*8), 7.51-7.39 (m, 6H, Ar-*H*7 and $\text{OCH}_2\text{Ar-H}$), 7.01 (d, J = 7.6 Hz, Ar-*H*6), 5.69 (s, 1H, ArC1-OH), 5.27 (s, 2H, OCH_2Ph); ^{13}C NMR (100 MHz, CDCl_3) δ 154.27, 145.62, 141.90, 134.47, 129.16, 128.39, 128.29, 127.77, 127.62, 126.49, 116.81, 107.35, 72.10.

5-Benzyloxy-2,3-dibromo-4-hydroxynaphthalen-1-yl *tert*-butyl carbonate (363)



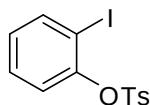
A solution of di-*tert*-butyl dicarbonate (109 mg, 0.5 mmol) in dichloromethane (1 mL) was added dropwise to a solution of **362** (212 mg, 0.5 mmol) and DMAP (3 mg, 0.025 mmol) in dichloromethane (10 mL) at $-20\text{ }^{\circ}\text{C}$, and the resulting mixture was stirred at this temperature for 2 hours. After this time, the solution was quenched with saturated aqueous ammonium chloride (5 mL) and further diluted with water (10 mL). The organic phase was washed with brine (20 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (3:2 dichloromethane / hexanes) to give the title product as an off-white crystalline solid (141 mg, 54%); R_f : 0.51 (2:1 dichloromethane/hexanes); mp $162\text{--}163\text{ }^{\circ}\text{C}$ (acetone); ^1H NMR (400 MHz, CDCl_3) δ 10.33 (s, 1H, Ar-OH), 7.53–7.45 (m, 7H, Ar-H), 7.03 (d, $J = 7.4\text{ Hz}$, 1H, Ar-H), 5.31 (s, 2H, ArCH₂O-), 1.62 (s, 9H, OC(CH₃)₃); ^{13}C NMR (100 MHz, CDCl_3) δ 154.61, 150.75, 150.38, 137.57, 134.28, 129.25, 129.04, 128.33, 127.90, 119.24, 115.50, 114.29, 107.09, 106.74, 84.47, 72.30, 53.46, 27.70; MS (CI, NH₃) m/z : 542 $[\text{M} + \text{NH}_4]^+$ (^{81}Br and ^{79}Br); HRMS (CI, NH₃) m/z calc. for $\text{C}_{22}\text{H}_{24}\text{N}^{79}\text{Br}_2\text{O}_5$: 540.0021 $[\text{M} + \text{NH}_4]^+$, found: 540.0027 $[\text{M} + \text{NH}_4]^+$; Elem. Anal. calc. for $\text{C}_{22}\text{H}_{20}\text{Br}_2\text{O}_5$: C 50.41%, H 3.85%, found: C 50.48%, H 3.79%.

2-Bromo-8-isopropoxynaphthalene-1,4-dione (504)¹⁸¹



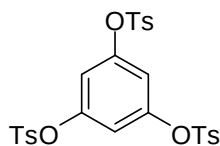
2-Iodopropane (3.0 mL, 5.09 g, 30.0 mmol) was added to a suspension of silver (I) oxide (6.95 g, 30.0 mmol) and **347** (2.53 g, 10.0 mmol) in chloroform (35 mL) and the resulting mixture was stirred for 18 hours. After this time, the mixture was filtered through Celite (which was washed with further portions of chloroform), concentrated under reduced pressure and the resulting residue was chromatographed (3:2 dichloromethane / hexanes) to furnish the title product as a yellow crystalline solid (2.12 g, 72%); R_f : 0.17 (dichloromethane/hexanes 2:1); mp: 72-73 °C (ethanol), lit.¹⁸¹ 73 °C; IR: $\nu_{\max}$ 2976, 2932, 1654, 1599, 1580, 1461, 1436, 1307, 1273, 1104, 821; ^1H NMR (400 MHz, CDCl_3) δ 7.67-7.60 (2H, m, Ar-*H5* and Ar-*H6*), 7.40 (s, 1H, C=CH-), 7.29 (dd, $J_1 = 7.3$ Hz, $J_2 = 2.2$ Hz, 1H, Ar-*H7*), 4.71 (sep., $J = 6.0$ Hz, 1H, -OCH(CH_3)₂), 1.44 (d, $J = 6.0$ Hz, 6H, -OCH(CH_3)₂); ^{13}C NMR (100 MHz, CDCl_3) δ 182.57, 175.80, 159.03, 142.17, 138.17, 135.13, 134.00, 120.77, 119.23, 72.23, 21.91; MS (CI, NH_3) m/z : 295 $[\text{M}]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{13}\text{H}_{12}^{79}\text{BrO}_3$ $[\text{M} + \text{H}]^+$: 294.9970, found: 294.9962.

2-Iodophenyl 4-methylbenzenesulfonate (393)¹⁸²



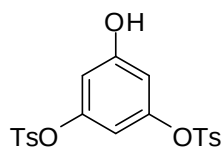
Tosyl chloride (2.00 g, 10.5 mmol) was added portionwise to a solution of 2-iodophenol (2.20 g, 10.0 mmol) in pyridine (10 mL) at 0 °C. The resulting mixture was warmed to room temperature, and stirred for 14 hours. After this time, water (50 mL) was added and the resulting precipitate was isolated by vacuum filtration and stirred in 6 M hydrochloric acid for 10 minutes. The solid was isolated by vacuum filtration, washed with cold methanol and recrystallised from dichloromethane/methanol to give the title compound as a white crystalline solid (3.18 g, 81%); R_f : 0.72 (3 : 2 hexanes / diethyl ether); mp 80-81 °C (dichloromethane/methanol), lit.¹⁸² 80-81 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.83 (d, J = 8.0 Hz, 2H, $\text{OSO}_2\text{Ar-H}$), 7.78 (d, J = 8.0 Hz, 1H, Ar- H), 7.35 (m, 4H, $\text{OSO}_2\text{Ar-H}$ and Ar- H), 7.00 (m, 1H, Ar- H), 2.48 (s, 3H, Ar- CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 150.03, 145.79, 140.11, 132.83, 129.85, 129.55, 128.88, 128.40, 123.04, 90.30, 21.82; MS (CI, NH_3) m/z : 392 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{13}\text{H}_{15}\text{NIO}_3\text{S}$: $[\text{M} + \text{NH}_4]^+$: 391.9817, found: 391.9821.

Benzene-1,3,5-triyl tris(4-methylbenzenesulfonate) (383)¹⁵⁵



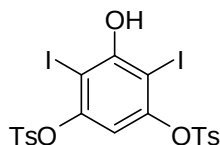
Tosyl chloride (157.3 g, 825 mmol) was added portionwise to a solution of phloroglucinol (31.53 g, 250 mmol) in pyridine (250 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred at this temperature for a further 14 hours. After this time, water (400 mL) was added, was added and the resulting precipitate was isolated by vacuum filtration and stirred in 6 M hydrochloric acid for 10 minutes. The solid was isolated by vacuum filtration, washed with cold methanol and recrystallised from dichloromethane/methanol to give the title compound as a white, crystalline solid (141.3 g, 96%); R_f : 0.44 (3:2 hexanes/diethyl ether); mp 85-86 °C (methanol), lit.¹⁸³ 84-86 °C; IR: $\nu_{\max}$ 1597, 1449, 1367, 1355, 1190, 1176, 983, 739, 659; ^1H NMR (400 MHz, CDCl_3) δ 7.63 (d, J = 8.0 Hz, 4H, -OSO₂Ar-*H*), 7.36 (d, J = 8.0 Hz, 4H, -OSO₂Ar-*H*), 6.62 (s, 3H, Ar-*H*), 2.49 (s, 9H, Ar-CH₃); ^{13}C NMR (100 MHz, CDCl_3) δ 149.80, 146.29, 131.44, 130.14, 128.42, 115.97, 21.83; HRMS (ESI) m/z calc. for C₂₇H₂₈NO₉S₃ [M + NH₄]⁺: 606.0926, found: 606.0933; Elem. Anal. calc. for C₂₇H₂₄O₉S₃: C 55.09%, H 4.11%, found: C 55.08% H 4.08%.

5-Hydroxy-1,3-phenylene bis(4-methylbenzenesulfonate) (384)¹⁵⁵



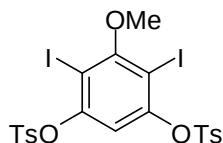
Potassium hydroxide (28.0 g, 500 mmol) in methanol (125 mL) and water (15 mL) was added slowly to a vigorously-stirred suspension of **383** (129.4 g, 220 mmol) in methanol (480 mL). Upon completion, the resulting mixture was stirred for a further 1 hour before being quenched with 2 M hydrochloric acid (375 mL) and diluted with water (300 mL). The resulting precipitate was isolated by vacuum filtration and recrystallised from toluene to give the title compound as a white, crystalline solid (77.63 g, 81%); R_f : 0.32 (3:2 hexanes/diethyl ether); mp 124-126 °C (toluene), lit.¹⁵⁵ 126-127 °C; IR: $\nu_{\max}$ 3418, 1596, 1356, 1189, 1173, 998, 816, 750; ^1H NMR (400 MHz, d_6 -acetone) δ 7.68 (d, J = 8.4 Hz, 4H, -OSO₂Ar-*H*), 7.34 (d, J = 8.0 Hz, 4H, OSO₂Ar-*H*), 6.49 (d, J = 2.0 Hz, 2H, Ar-*H*4 and Ar-*H*6), 6.21 (t, J = 2.0 Hz, 1H, Ar-*H*2), 2.47 (s, 6H, Ar-CH₃); ^{13}C NMR (100 MHz, d_6 -acetone) δ 158.99, 150.32, 140.86, 133.52, 130.23, 129.94, 108.75, 107.65, 28.99; MS (CI, NH₃) m/z : 452 [$\text{M} + \text{NH}_4$]⁺; HRMS (CI, NH₃) m/z calc. for C₂₀H₂₂NO₇S₂ [$\text{M} + \text{NH}_4$]⁺: 452.0838, found: 452.0839, Elem. Anal. calc. for C₂₀H₁₆I₂O₇S₂: C 35.00%, H 2.35%, S 9.34%, found: C 35.06%, H 2.38% S 9.38%.

5-Hydroxy-4,6-diiodo-1,3-phenylene bis(4-methylbenzenesulfonate) (385)



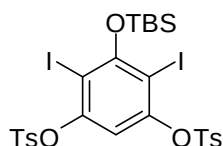
A solution of **384** (2.17 g, 5.0 mmol) and *N*-iodosuccinimide (2.36 g, 10.5 mmol) in chloroform (20 mL) was heated at 40 °C for 18 hours, after which time the mixture was cooled, filtered and the filtrate was washed with saturated aqueous sodium thiosulfate (2 x 20 mL), brine (20 mL), dried over magnesium sulfate, concentrated under reduced pressure. The resulting solid was triturated in diethyl ether/hexane (3:1, 10 mL) at 0 °C for 1 hour to deliver the title compound as a white, crystalline solid (4.68 g, 65%); R_f : 0.48 (1:1 hexanes/diethyl ether); mp 148-150 °C (diethyl ether/hexane); IR: $\nu_{\max}$ 3453, 1596, 1560, 1385, 1355, 1190, 1173, 1028, 1001, 813, 772, 750, 662; ^1H NMR (400 MHz, CDCl_3) δ 7.82 (d, J = 8.4 Hz, 4H, $-\text{OSO}_2\text{Ar-H}$), 7.36 (d, J = 8.0 Hz, 4H, $-\text{OSO}_2\text{Ar-H}$), 6.93 (s, 1H, Ar-*H*), 2.47 (s, 6H, Ar- CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 156.19, 151.00, 146.36, 132.21, 130.13, 128.89, 108.81, 78.12, 21.88; HRMS (ESI) m/z calc. for $\text{C}_{20}\text{H}_{17}\text{I}_2\text{O}_7\text{S}_2$ $[\text{M} + \text{H}]^+$: 686.8505, found: 686.8504; Elem. Anal. calc. for $\text{C}_{20}\text{H}_{16}\text{I}_2\text{O}_7\text{S}_2$: C 35.00%, H 2.34%, S 9.34%, found: C 35.06%, H 2.38% S 9.38%.

4,6-Diiodo-5-methoxy-1,3-phenylene bis(4-methylbenzenesulfonate) (391)¹⁵⁶



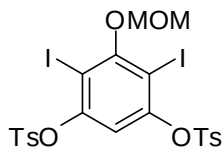
Dimethyl sulfate (157 μ L, 1.7 mmol) was added to a suspension of caesium carbonate (1.11 g, 3.2 mmol) and **385** (1.03 g, 1.5 mmol) in acetone (3 mL) at 0 $^{\circ}$ C. The resulting mixture was then warmed to room temperature and stirred for 14 hours. After this time, diethylamine (300 μ L) was added and the mixture stirred for a further 30 minutes, before being quenched with 2 M hydrochloric acid, extracted into ethyl acetate (10 mL), washed with saturated aqueous sodium hydrogen carbonate (10 mL), brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (3:1 dichloromethane/hexanes) to give the title product as a white, crystalline solid (903 mg, 87%); R_f : 0.55 (2:1 hexanes/ethyl acetate); mp 141-143 $^{\circ}$ C (hexanes/ethyl acetate), lit.¹⁵⁶ 142.8-143.1 $^{\circ}$ C; ^1H NMR (400 MHz, CDCl_3) δ 7.82 (d, J = 8.4 Hz, 4H, $\text{OSO}_2\text{Ar-H}$), 7.36 (d, J = 8.0 Hz, 4H, $\text{OSO}_2\text{Ar-H}$), 7.13 (s, 1H, Ar-H), 3.75 (s, 3H, Ar- OCH_3), 2.47 (s, 6H, Ar- CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 161.63, 151.36, 146.31, 132.31, 130.08, 128.91, 112.77, 86.72, 60.86, 21.86; HRMS (ESI) m/z calc. for $\text{C}_{21}\text{H}_{19}\text{I}_2\text{O}_7\text{S}_2$ $[\text{M} + \text{H}]^+$: 700.8662, found: 700.8660.

5-*tert*-Butyldimethylsilyloxy-4,6-diiodo-1,3-phenylene bis(4-methylbenzenesulfonate) (392)



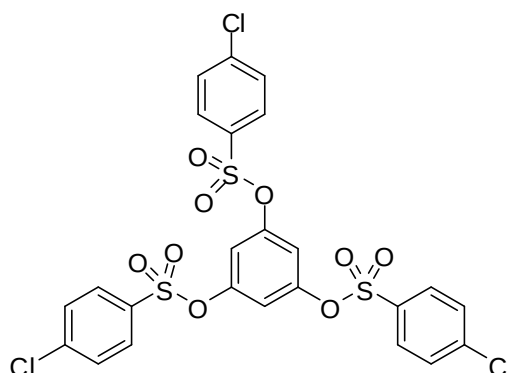
tert-Butyldimethylchlorosilane (362 mg, 2.4 mmol) was added to a stirred solution of **385** (1.37 g, 2.0 mmol) and triethylamine (419 μ L, 3.0 mmol) in dichloromethane (5 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 14 hours. After this time, water (5 mL) was added, and the organic phase washed with water (5 mL), brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (3:2 dichloromethane/hexanes) to give the title compound as a white solid (1.38 g, 86%); R_f : 0.50 (8:1 hexanes/ethyl acetate); mp 182-183 °C (ethyl acetate/hexanes); IR: $\nu_{\max}$ 2944, 2865, 1561, 1421, 1353, 1168, 1092, 1027, 806, 727, 688, 662; ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, J = 8.4 Hz, 4H, $\text{OSO}_2\text{Ar-H}$), 7.37 (d, J = 8.4 Hz, 4H, $\text{OSO}_2\text{Ar-H}$), 7.12 (s, 1H, Ar-H), 2.49 (s, 6H, Ar- CH_3), 0.99 (s, 9H, Si- $\text{C}(\text{CH}_3)_3$), 0.34 (s, 6H, Si- CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 158.28, 151.25, 146.11, 132.35, 129.98, 129.00, 109.84, 85.15, 26.47, 21.83, 18.95, 0.05; HRMS (ESI) m/z calc. for $\text{C}_{26}\text{H}_{31}\text{I}_2\text{O}_7\text{S}_2\text{Si}$ $[\text{M} + \text{H}]^+$: 800.9370, found: 800.9388; Elem. Anal. calc. for $\text{C}_{26}\text{H}_{30}\text{I}_2\text{O}_7\text{S}_2\text{Si}$: C 39.01%, H 3.78%, S 8.01%, found: C 39.06%, H 3.80%, S 7.88%.

4,6-Diiodo-5-(methoxymethoxy)-1,3-phenylene bis(4-methylbenzenesulfonate)
(410)



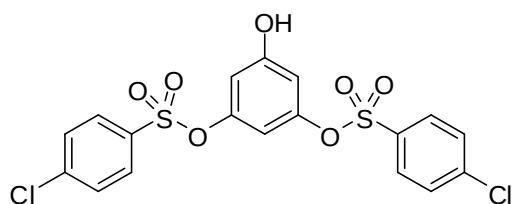
Methyl chloromethyl ether (3.04 mL, 40 mmol) was added dropwise to a solution of **385** (4.34 g, 10.0 mmol) and diethyl-*iso*-propylamine (3.05 mL, 17.5 mmol) in dichloromethane (40 mL) at 0 °C. The resulting mixture was stirred at room temperature for 14 hours before being diluted with water (40 mL). The organic phase was separated, dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (2:1 hexanes/ethyl acetate) to yield the title compound as a white, crystalline solid (6.05 g, 83%); R_f : 0.42 (2:1 hexanes/ethyl acetate); mp 114-115 °C (hexanes/ethyl acetate); IR: $\nu_{\max}$ 3452, 2924, 2856, 1595, 1561, 1382, 1355, 1191, 1174, 1026, 1001, 772, 751, 705, 664; ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, J = 8.4 Hz, 4H, $\text{OSO}_2\text{Ar-H}$), 7.38 (d, J = 8.4 Hz, 4H, $\text{OSO}_2\text{Ar-H}$), 7.19 (s, 1H, Ar- H), 5.06 (s, 2H, ArOCH_2), 3.69 (s, 3H, $\text{ArOCH}_2\text{OCH}_3$), 2.50 (s, 3H, Ar- CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 159.11, 151.42, 146.32, 132.29, 130.08, 128.92, 112.80, 100.32, 87.75, 59.00, 21.85; MS (CI, NH_3) m/z : 748 $[\text{M} + \text{NH}_4]^+$; HRMS (ESI) m/z calc. for $\text{C}_{22}\text{H}_{24}\text{I}_2\text{O}_8\text{S}_2$ $[\text{M} + \text{NH}_4]^+$: 747.9033, found: 747.9031; Elem. Anal. calc. for $\text{C}_{22}\text{H}_{20}\text{I}_2\text{O}_8\text{S}_2$: C 36.18%, H 2.76%, S 8.78%, found: C 36.19%, H 2.70%, S 8.70%.

Benzene-1,3,5-triyl tris(4-chlorobenzenesulfonate) (402)



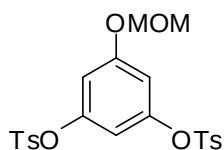
4-chlorobenzenesulfonyl chloride (110.8 g, 525 mmol) was added to a solution of phloroglucinol **382** (18.92 g, 150 mmol) in pyridine (150 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred at this temperature for a further 14 hours. After this time, water (300 mL) was added and the resulting precipitate was isolated by vacuum filtration and stirred in 6 M hydrochloric acid for 10 minutes. The solid was isolated by vacuum filtration, washed with cold methanol and recrystallised from dichloromethane/methanol to give the title compound as a white, crystalline solid (86.03 g, 88%); R_f : 0.58 (1:1 hexanes/ethyl acetate); mp 117-118 °C (methanol); IR: $\nu_{\max}$ 1735, 1597, 1584, 1381, 1357, 110, 1174, 1084, 970, 874, 765, 728; ^1H NMR (400 MHz, CDCl_3) δ 7.75 (d, J = 8.4 Hz, 6H, $\text{OSO}_2\text{Ar-H}$), 7.58 (d, J = 8.8 Hz, 6H, $\text{OSO}_2\text{Ar-H}$), 6.73 (s, 3H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3) δ 149.67, 141.90, 132.92, 129.99, 129.81, 116.01; HRMS (CI, NH_3) m/z calc. for $\text{C}_{24}\text{H}_{19}^{35}\text{Cl}_3\text{NO}_9\text{S}_3$ $[\text{M} + \text{NH}_4]^+$: 665.9288, found: 665.9269; Elem. Anal. calc. for $\text{C}_{24}\text{H}_{15}^{35}\text{Cl}_3\text{O}_9\text{S}_3$: C 44.35%, H 2.33%, found: C 44.35%, H 2.34%.

5-Hydroxy-1,3-phenylene bis(4-chlorobenzenesulfonate) (**403**)



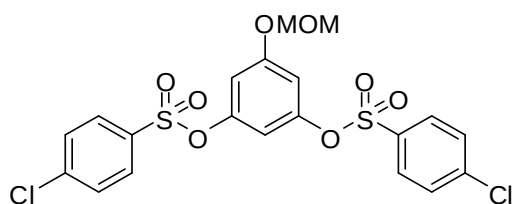
Potassium hydroxide (2.16 g, 38.6 mmol) in methanol (9.5 mL) and water (0.5 mL) was added slowly to a vigorously stirred suspension of **402** (14.72 g, 17.0 mmol) in methanol (55 mL). Upon completion, the resulting mixture was stirred for a further 1 hour before being quenched with 2 M hydrochloric acid (60 mL) and diluted with water (60 mL). The resulting precipitate was isolated by vacuum filtration and recrystallised from toluene to give the title compound as a white, crystalline solid (8.08 g, 75%); R_f : 0.58 (1:1 hexanes/ethyl acetate); mp 116-117 °C (toluene); IR: $\nu_{\max}$ 3418, 1617, 1597, 1475, 1457, 1357, 1344, 1186, 1172, 1087, 985, 867, 817, 784, 657; ^1H NMR (400 MHz, CDCl_3) δ 7.78 (d, J = 8.4 Hz, 2H, $\text{OSO}_2\text{Ar-H}$), 7.56 (d, J = 8.8 Hz, 2H, $\text{OSO}_2\text{Ar-H}$), 6.54 (t, J = 2.0 Hz, 2H, Ar-H4 and Ar-H6), 6.26 (d, J = 2.0 Hz, 1H, Ar-H2), 5.92 (br. s, 1H, Ar-OH); ^{13}C NMR (100 MHz, CDCl_3) δ 157.35, 150.02, 141.62, 133.18, 129.83, 109.15, 108.66; MS (CI, NH_3) m/z : 492 [$\text{M} - \text{H} + \text{NH}_4$] $^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{18}\text{H}_{16}\text{Cl}_2\text{NO}_7\text{S}_2$ [$\text{M} + \text{NH}_4$] $^+$: 491.9745, found: 491.9766; Elem. Anal. calc. for $\text{C}_{18}\text{H}_{12}^{35}\text{Cl}_2\text{O}_7\text{S}_2$: C 45.48%, H 2.54%, S 13.49%, found: C 45.47%, H 2.46%, S 13.36%.

5-Methoxymethoxy-1,3-phenylene bis(4-methylbenzenesulfonate) (406)



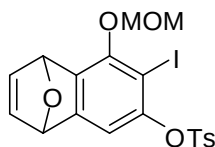
Methyl chloromethyl ether (2.28 mL, 30.0 mmol) was added dropwise to a solution of phenol **384** (4.34 g, 10.0 mmol) and di-*iso*-propylethylamine (2.61 mL, 15.0 mmol) in dichloromethane (40 mL) at 0 °C. The resulting mixture was stirred at room temperature for 14 hours before being diluted with water (40 mL). The organic phase was separated, dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (2:1 hexanes/ethyl acetate) to yield the title compound as a white, crystalline solid (6.05 g, 81%); R_f : 0.39 (2:1 hexanes/ethyl acetate); mp 96-97 °C (ethyl acetate/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, J = 8.4 Hz, 4H, $\text{OSO}_2\text{Ar-H}$), 7.36 (d, J = 8.4 Hz, 4H, $\text{OSO}_2\text{Ar-H}$), 6.62 (d, J = 2.0 Hz, 2H, Ar- H_4 , Ar- H_6), 6.36 (t, J = 2.0 Hz, 1H, Ar- H_2), 5.00 (s, 2H, Ar- OCH_2OCH_3), 3.38 (s, 3H, Ar- OCH_2OCH_3), 2.49 (s, 3H, Ar- CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 158.18, 150.17, 145.78, 131.97, 129.92, 128.51, 110.22, 109.64, 94.58, 56.19, 21.77; MS (CI, NH_3) m/z : 536 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{20}\text{H}_{16}^{35}\text{Cl}_2\text{O}_8\text{S}_2$ $[\text{M} + \text{NH}_4]^+$: 536.007, found: 536.0021; Elem. Anal. calc. for $\text{C}_{22}\text{H}_{22}\text{O}_8\text{S}_2$: C 55.22%, H 4.63%, S 13.40%, found: C 55.29%, H 4.57% S 13.28%.

5-(Methoxymethoxy)-1,3-phenylene bis(4-chlorobenzenesulfonate) (408)



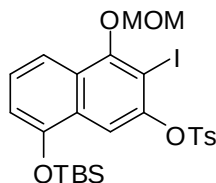
Methyl chloromethyl ether (2.28 mL, 30.0 mmol) was added dropwise to a solution of **403** (4.75 g, 10.0 mmol) and di-*iso*-propylethylamine (2.61 mL, 15.0 mmol) in dichloromethane (40 mL) at 0 °C. The resulting mixture was stirred at room temperature for 14 hours before being diluted with water (40 mL). The organic phase was separated, dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (2:1 hexanes/ethyl acetate) to yield the title compound as a white, crystalline solid (4.11 g, 79%); R_f : 0.73 (2:1 hexanes/ethyl acetate); mp 102-103 °C (ethyl acetate/hexanes); IR: $\nu_{\max}$ 1613, 1587, 1377, 1188, 1013, 984, 773; ^1H NMR (400 MHz, CDCl_3) 7.78 (d, J = 8.4 Hz, 4H, $\text{OSO}_2\text{Ar-H}$), 7.56 (d, J = 8.4 Hz, 4H, $\text{OSO}_2\text{Ar-H}$), 6.64 (d, J = 2.3 Hz, 2H, Ar- H_4 , Ar- H_6), 6.42 (t, J = 2.0 Hz, 1H, Ar- H_2), 5.03 (s, 2H, Ar- OCH_2OCH_3), 3.40 (s, 3H, Ar- OCH_2OCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 158.42, 149.96, 141.41, 133.90, 129.89, 129.72, 109.98, 109.72, 94.61, 56.30; MS (CI, NH_3) m/z : 496 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{22}\text{H}_{20}^{35}\text{Cl}_2\text{NO}_8\text{S}_2$ $[\text{M} + \text{NH}_4]^+$: 496.1100, found: 496.1111; Elem. Anal. calc. for $\text{C}_{20}\text{H}_{16}\text{Cl}_2\text{O}_8\text{S}_2$: C 46.25%, H 3.11%, S 12.35%, found: C 46.32%, H 2.92%, S 12.19%.

Toluene-4-sulfonic acid 5-iodo-6-methoxymethoxy-11-oxatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5,9-tetraen-4-yl ester (412)



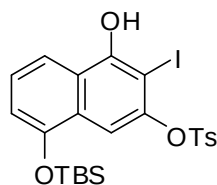
A solution of *iso*-propylmagnesium chloride (2.0 M in THF, 1.0 mL, 2.0 mmol) was added dropwise to a solution of **410** (1.46 g, 2.0 mmol) in THF (8 mL) at -78°C . The resulting solution was stirred at this temperature for 1 hour before being rapidly warmed to room temperature and stirred for a further 16 hours. After this time, saturated aqueous ammonium chloride was added, followed by ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (2:1 hexanes/ethyl acetate) to yield the title compound as a white solid (546 mg, 55%); R_f : 0.35 (2:1 hexanes/ethyl acetate); mp $84-86^{\circ}\text{C}$ (ethyl acetate/hexanes); IR: ν_{max} 2944, 2866, 1563, 1421, 1333, 1168, 1092, 808, 727, 687, 661; ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, $J = 8.4$ Hz, 2H, $\text{OSO}_2\text{Ar-H}$), 7.36 (d, $J = 8.4$ Hz, 2H, $\text{OSO}_2\text{Ar-H}$), 7.11 (s, 1H, Ar-*H*), 7.04 (app. s, 2H, HC=CH), 6.03 (s, 1H, O-*CH-CH=CH-*), 5.71 (s, 1H, O-*CH-CH=CH-*), 5.23 (d, $J = 7.2$ Hz, 1H, Ar- $\text{OCH}_2\text{-OCH}_3$), 4.96 (d, $J = 6.8$ Hz, 1H, Ar- $\text{OCH}_2\text{-OCH}_3$), 3.58 (s, 3H, Ar- $\text{OCH}_2\text{-OCH}_3$), 2.48 (s, 3H, Ar- CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 153.32, 150.01, 148.57, 145.73, 142.78, 142.65, 135.37, 132.86, 129.91, 129.78, 111.34, 97.20, 84.96, 84.96, 82.30, 81.83, 56.96, 21.79; MS (CI, NH_3) m/z : 518 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3), m/z calc. for $\text{C}_{19}\text{H}_{21}\text{INO}_6\text{S}$ $[\text{M} + \text{NH}_4]^+$: 518.0134, found: 518.0133; Elem. Anal. calc. for $\text{C}_{19}\text{H}_{17}\text{IO}_6\text{S}$: C 45.61%, H 3.42%, S 6.41%, found: C 45.59%, H 3.39%, S 6.40%.

8-*tert*-Butyldimethylsilyloxy-3-iodo-4-methoxymethoxy)naphthalen-2-yl 4-methylbenzenesulfonate (414)



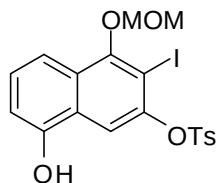
tert-Butyldimethylsilyl triflate (432 μ L, 1.8 mmol) was added dropwise to a solution of **412** (470 mg, 0.9 mmol) and 2,6-lutidine (547 μ L, 4.7 mmol) in dichloromethane (4 mL) at -78°C . The resulting solution was warmed to room temperature and stirred for 18 hours, before being quenched with water (2 mL). The mixture was further diluted with water (5 mL) and dichloromethane (5 mL) and the organic phase washed with 1 M aqueous sodium hydrogensulfate (2 x 10 mL), brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (6:1 hexanes/ethyl acetate) to yield the title compound as a pale yellow oil (306 mg, 53%); R_f : 0.76 (2:1 hexanes/ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 8.02 (s, 1H, Ar-*H1*), 7.86 (d, J = 8.4 Hz, 2H, $\text{OSO}_2\text{Ar-H}$), 7.76 (d, J = 8.8 Hz, 2H, $\text{OSO}_2\text{Ar-H}$), 7.41 (t, J = 8.0 Hz, 1H, Ar-*H6*), 7.32 (d, J = 8.4 Hz, 1H, Ar-*H5*), 6.96 (d, J = 7.6 Hz, 1H, Ar-*H7*), 5.20 (s, 2H, Ar- $\text{OCH}_2\text{-OCH}_3$), 3.73 (s, 3H, Ar- $\text{OCH}_2\text{-OCH}_3$), 2.44 (s, 3H, Ar- CH_3), 1.10 (s, 9H, $-\text{SiC}(\text{CH}_3)_3$), 0.31 (s, 6H, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 156.34, 151.90, 146.35, 145.78, 132.88, 129.82, 128.97, 128.77, 128.47, 127.32, 115.36, 114.48, 111.92, 100.77, 87.41, 58.41, 53.68, 25.69, 21.63, 18.28, -4.49 ; MS (CI, NH_3) m/z : 614 $[\text{M}]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{25}\text{H}_{31}\text{IO}_6\text{SSi}$ $[\text{M}]^+$: 614.0655, found: 614.0654.

8-*tert*-Butyldimethylsilyloxy-4-hydroxy-3-iodonaphthalen-2-yl 4-methylbenzenesulfonate (416)



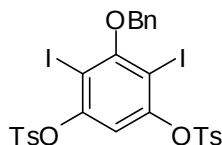
Trifluoroacetic acid (23 μ L, 0.3 mmol) was added to a solution of **416** (362 mg, 0.6 mmol) in dichloromethane (5 mL) and stirred at room temperature for 5 hours. After this time, the mixture was diluted with water (5 mL) and the organic phase was washed with brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (3:1 hexanes/ethyl acetate) to yield the title compound as a pale yellow solid (256 mg, 76%); R_f : 0.71 (2:1 hexanes/ethyl acetate); mp 129-130 $^{\circ}$ C (ethyl acetate/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.86 (d, J = 8.4 Hz, $\text{OSO}_2\text{Ar-H}$, 2H), 7.82 (d, J = 8.4 Hz, 1H, Ar- H_5), 7.70 (s, 1H, Ar- H_1), 7.36 (m, 2H, $\text{OSO}_2\text{Ar-H}$ and 1H, Ar- H_6), 6.96 (d, J = 8.0 Hz, 1H, Ar- H_7), 5.94 (br. s, 1H, Ar-OH), 2.47 (s, 3H, Ar- CH_3), 1.07 (s, 9H, $\text{SiC}(\text{CH}_3)_3$), 0.28 (s, 6H, $-\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (100 MHz, CDCl_3) δ 153.16, 151.63, 145.55, 133.07, 29.85, 128.80, 126.67, 123.46, 115.51, 114.97, 107.94, 25.83, 21.79, 18.37, -4.32; MS (CI, NH_3) m/z : 588 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{23}\text{H}_{28}\text{IO}_5\text{SSi}$: 571.0472 $[\text{M} + \text{H}]^+$, found: 571.0472 $[\text{M} + \text{H}]^+$; Elem. Anal. calc. for $\text{C}_{23}\text{H}_{27}\text{IO}_5\text{SSi}$: C 48.42%, H 4.77%, S 5.62% found: C 48.48%, H 4.81%, S 5.53%.

8-Hydroxy-3-iodo-4-(methoxymethoxy)naphthalene-2-yl 4-methylbenzenesulfonate (417)



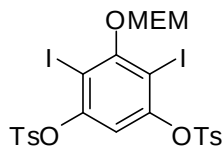
Trimethylsilyl trifluoromethanesulfonate (1.45 mL, 8.0 mmol) was added dropwise to a solution of **412** (1.00 g, 2.0 mmol) and 2,6-lutidine (1.86 g, 16.0 mmol) in dichloromethane (10 mL) at 0 °C. The resulting solution was warmed to room temperature and stirred for 3 hours before being quenched with water (10 mL). The organic phase was washed with 1 M aqueous sodium hydrogen sulfate (2 x 10 mL), brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure. The resulting residue was dissolved in THF (8 mL) and TBAF (1.0 M in THF, 4 mL) was added at 0 °C. After 20 minutes, water (10 mL) was added and the mixture extracted into ethyl acetate (2 x 10 mL). The organic phase was washed with brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and chromatographed (2:1 hexanes/ethyl acetate) to obtain the title compound as a yellow solid (542 mg, 54%); R_f : 0.31 (2:1 hexanes/ethyl acetate); mp 102-103 °C (methanol); 3393, 1585, 1454, 1376, 1189, 1157, 1090, 1017, 730; ^1H NMR (400 MHz, CDCl_3) δ 7.98 (s, 1H, Ar-H1); 7.85 (d, J = 8.0 Hz, 2H, -OSO₂Ar-H), 7.67 (d, 1H, J = 8.4 Hz, Ar-H5); 7.35-7.30 (m, 2H, -OSO₂Ar-H, and 1H, Ar-H5); 6.87 (d, J = 9.6 Hz, 1H, Ar-H7); 5.93 (br. s, 1H, Ar-OH); 5.16 (s, 2H, Ar-OCH₂OCH₃); 3.70 (s, 3H, Ar-OCH₂OCH₃); 2.44 (s, 3H, Ar-CH₃); ^{13}C NMR (100 MHz, CDCl_3) δ 156.09, 151.92, 146.06, 145.81, 132.73, 129.80, 129.01, 128.80, 127.34, 124.99, 114.85, 111.76, 110.52, 100.64, 87.55, 58.57, 21.79; MS (CI, NH_3) m/z : 518 ($\text{M} + \text{NH}_4$); HRMS (CI, NH_3) m/z calc. for $\text{C}_{19}\text{H}_{21}\text{INO}_6\text{S}$ [$\text{M} + \text{NH}_4$]⁺: 518.0134, found 518.0115.

5-(Benzyloxy)-4,6-diiodo-1,3-phenylene bis(4-methylbenzenesulfonate) (437)



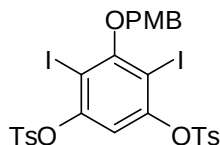
Benzyl bromide (4.8 mL) was added dropwise to a suspension of phenol **385** (13.91 g, 20.2 mmol) and caesium carbonate (9.87 g, 30.3 mmol) in THF (60 mL) at 0 °C. The resulting solution was warmed to room temperature and stirred for 18 hours, before being diluted with water (50 mL) and extracted into ethyl acetate (2 x 50 mL). The organic phases were washed with brine (50 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (2:1 hexanes/ethyl acetate) to give the title product as a white, crystalline solid (15.75 g, 91%); mp (dichloromethane/methanol) 142-143 °C; R_f : 0.80 (1:1 hexanes/ethyl acetate); IR: $\nu_{\max}$ 2944, 2866, 1562, 1421, 1337, 1167, 1092, 770, 728, 688, 662; ^1H NMR (400 MHz, CDCl_3): δ 7.83 (d, J = 6.1 Hz, 4H, $\text{OSO}_2\text{Ar-H}$), 7.58 (dd, J_1 = 7.8 Hz, J_2 = 1.35 Hz, Ar- H), 7.42-7.35 (m, 7H, $\text{OCH}_2\text{Ar-H}$ and $\text{OSO}_2\text{Ar-H}$), 7.21 (s, 1H, Ar- H), 4.90 (s, 2H, OCH_2Ph), 2.47 (s, 3H, Ar- CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 160.01, 151.47, 146.34, 135.43, 132.30, 130.09, 128.95, 128.68, 128.53, 112.98, 87.35, 74.57, 21.86; MS (CI, NH_3) m/z : 796 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{27}\text{H}_{22}\text{I}_2\text{O}_7\text{S}_2$ $[\text{M} + \text{H}]^+$: 776.8975, found: 776.8967; Elem. Anal. calc. for $\text{C}_{27}\text{H}_{21}\text{I}_2\text{O}_7\text{S}_2$: C 41.77%, H 2.86%, S 8.26%, found: C 41.71%, H 2.80%, S 8.17%.

4,6-Diiodo-5-(2-methoxyethoxy)methoxy-1,3-phenylene bis(4-methylbenzenesulfonate) (438)



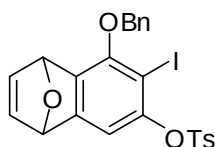
Methoxyethoxymethyl chloride (1.03 mL, 9.0 mmol) was added dropwise to a solution of phenol **385** (2.06 g, 3.0 mmol) and di-*iso*-propylethylamine (914 μ L) in dichloromethane (15 mL) at 0 °C. The solution was then warmed to room temperature and stirred for 18 hours, after which time it was quenched with water (10 mL). The organic phase was washed with further water (10 mL), brine (10 mL), concentrated under reduced pressure and the resulting residue was chromatographed to yield the title compound (1.92 g, 82%) as a white, crystalline solid; R_f : 0.52 (1:1 hexanes/ethyl acetate); mp 108-109 °C (dichloromethane/methanol); IR: $\nu_{\max}$ 2920, 2870, 1597, 1376, 1356, 1193, 1173, 1158, 1027, 1008, 813, 754, 658; ^1H NMR (400 MHz, CDCl_3) δ 7.81 (J = 8.3 Hz, 4H, $\text{OSO}_2\text{Ar-H}$), 7.35 (J = 8.3 Hz, 4H, $\text{OSO}_2\text{Ar-H}$), 7.16 (s, 1H, Ar- H), 5.12 (s, 1H, Ar-O- CH_2O), 4.03 (m, 2H, O- $\text{CH}_2\text{CH}_2\text{O}$), 3.58 (m, 2H, $\text{OCH}_2\text{CH}_2\text{O}$), 3.38 (s, 3H, ArOCH_3), 2.47 (s, 6H, Ar- CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ : 158.88, 151.42, 146.32, 132.30, 130.08, 128.92, 112.81, 99.09, 87.69, 71.53, 70.46, 59.14, 21.84; MS (CI, NH_3) m/z : 792 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{24}\text{H}_{28}\text{I}_2\text{NO}_9\text{S}_2$ $[\text{M} + \text{NH}_4]^+$: 791.9295 found: 791.9289; Elem. Anal. calc. for $\text{C}_{24}\text{H}_{24}\text{I}_2\text{O}_9\text{S}_2$: C 37.22%, H 3.12%, S 8.28%, found: C 37.16%, H 3.11%, S 8.37%.

4,6-Diiodo-5-(4-methoxybenzyloxy)-1,3-phenylene bis(4-methylbenzenesulfonate)
(439)



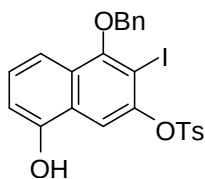
4-Methoxybenzyl chloride (2.71 mL, 20 mmol) was added dropwise to a suspension of **385** (6.86 g, 10 mmol), *tert*-butylammonium iodide (923 mg, 2.5 mmol) and caesium carbonate (4.89 g, 15 mmol) in THF (30 mL). The resulting mixture was heated under reflux for 12 hours, before being cooled and diluted with water (30 mL) and extracted into ethyl acetate. The organic phase was washed with brine (30 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (2:1 hexanes/ethyl acetate) to deliver the title compound as a white, crystalline solid (1.32 g, 82%); R_f : 0.45 (2:1 hexanes/ethyl acetate); mp 148-149 °C (dichloromethane / methanol); ^1H NMR (CDCl_3 , 400 MHz): δ 7.82 (d, J = 8.4 Hz, 4H, OSO_2ArH), 7.51 (d, J = 8.8 Hz, 2H, MeOAr-H), 7.36 (d, J = 8.4 Hz, 4H, OSO_2ArH), 7.19 (s, 1H, Ar-H), 6.91 (d, J = 8.8 Hz, 2H, MeOAr-H), 4.83 (s, 2H, ArCH_2O), 3.82 (s, 3H, Ar-OCH_3), 2.46 (s, 4H, Ar-CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ : 159.50, 150.90, 145.81, 131.74, 129.91, 129.57, 128.43, 126.99, 113.40, 112.41, 87.00, 73.96, 54.84, 21.35; HRMS (ESI) m/z calc. for $\text{C}_{28}\text{H}_{24}\text{I}_2\text{NaO}_8\text{S}_2$ $[\text{M} + \text{Na}]^+$: 828.8900 found: 828.8915; Elem. Anal. calc. for $\text{C}_{28}\text{H}_{24}\text{I}_2\text{O}_8\text{S}_2$: C 41.70%, H 3.00%, S 7.95%, found: C 41.78%, H 2.92%, S 8.00%.

Toluene-4-sulfonic acid 5-iodo-6-benzyloxy-11-oxa-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5,9-tetraen-4-yl ester (440)



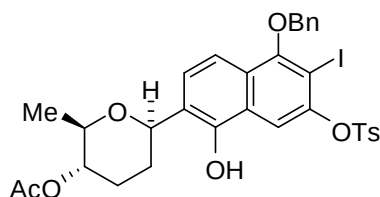
A solution of *iso*-propylmagnesium chloride (2.0 M in THF, 1.7 mL, 3.3 mmol) was added slowly to a solution of **437** (2.56 g, 3.3 mmol) and furan (1.82 mL, 26.4 mmol) in THF (13 mL) at $-78\text{ }^{\circ}\text{C}$, and the resulting solution was stirred at this temperature for a further 45 minutes. After this time, the solution was allowed to warm to room temperature and stirred for a further 18 hours. After this time, saturated aqueous ammonium chloride (20 mL) was added, and the mixture extracted into ethyl acetate (2 x 20 mL). The organic phase was washed with brine (20 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (2:1 hexanes/ethyl acetate) in order to obtain the title product as a white, crystalline solid (1.10 g, 61 %); mp $160\text{--}162\text{ }^{\circ}\text{C}$ (dichloromethane/methanol); R_f : 0.49 (2:1 hexanes/ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 7.86 (d, $J = 8.4$ Hz, 2H, $\text{OSO}_2\text{Ar-H}$), 7.47–7.39 (m, 5H, $\text{OCH}_2\text{Ar-H}$), 7.36 (d, $J = 8.0$ Hz, 2H, $\text{OSO}_2\text{Ar-H}$), 7.14 (s, 1H, Ar-H), 6.99 (dd, $J_1 = 5.2$ Hz, $J_2 = 2.0$ Hz, 1H, OCHCH=CHCHO), 6.62 (dd, $J_1 = 5.4$ Hz, $J_2 = 1.6$ Hz, 1H, OCHCH=CHCHO), 5.80 (m, 1H, OCHCH=CHCHO), 5.68 (m, 1H, O-CHCH=CHCHO), 5.10 (s, 2H, OCH_2Ar), 2.49 (s, 3H, ArCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 153.17, 151.45, 148.72, 145.78, 142.69, 142.32, 136.16, 135.79, 132.83, 129.80, 128.92, 128.74, 128.51, 127.88, 111.48, 85.20, 82.21, 81.24, 75.22, 21.83; MS (CI, NH_3) m/z : 564 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{24}\text{H}_{20}\text{IO}_5\text{S}$ $[\text{M} + \text{H}]^+$: 547.0076, found 547.0067, calc. for $\text{C}_{24}\text{H}_{23}\text{INO}_5\text{S}$ $[\text{M} + \text{NH}_4]^+$: 564.0342, found: 564.0334; Elem. Anal. calc. for $\text{C}_{24}\text{H}_{19}\text{IO}_5\text{S}$: C 52.76%, H 3.51%, S 5.87%, found: C 52.83%, H 3.53%, S 5.93%.

4-Benzyloxy-8-hydroxy-3-iodo-naphthalen-2-yl 4-methylbenzenesulfonate (441)



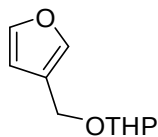
Trimethylsilyl trifluoromethanesulfonate (450 μ L, 2.5 mmol) was added dropwise at -78°C to a solution of cycloadduct **440** (340 mg, 0.6 mmol) and 2,6-lutidine (433 μ L, 5.0 mmol) in dichloromethane (3 mL), before being warmed to room temperature and stirred for 14 hours. After this time water (5 mL) was added, and the organic phase was washed with 1 M sodium hydrogen sulfate (2 x 5 mL) and brine (5 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was redissolved in THF (1 mL) and TBAF (1 M in THF, 2.5 mL, 2.5 mmol) was added dropwise. The solution was stirred for a further 10 minutes, before water (5 mL) was added and the solution was extracted into ethyl acetate (2 x 10 mL). The organic phase was washed with brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (4:1 hexanes/ethyl acetate) to yield the title compound as an off-white solid (207 mg, 61%); R_f : 0.40 (2:1 hexanes/ethyl acetate); mp $57\text{--}58^{\circ}\text{C}$ (ethyl acetate/hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 8.05 (s, 1H, Ar-*H1*), 7.90 (d, $J = 8.4$ Hz, 2H, $\text{OSO}_2\text{Ar-H}$), 7.68–7.64 (m, 2H *H*-ArCH₂O and 1H, Ar-*H5*), 7.49–7.32 (m, 2H, $\text{OSO}_2\text{Ar-H}$ and 1H, Ar-*H6* and 3H, *H*-Ar-CH₂O), 6.91 (d, $J = 7.2$ Hz, 1H, Ar-*H7*), 5.65 (br. s, 1H, Ar-OH), 5.04 (s, 2H, PhCH₂O), 2.48 (s, 3H, Ar-CH₃); ^{13}C NMR (CDCl_3 , 100 MHz): δ 156.99, 152.08, 146.22, 145.68, 136.40, 132.85, 129.75, 128.99, 128.59, 128.41, 128.18, 127.29, 125.07, 114.76, 111.59, 110.45, 87.47, 75.73, 21.76; HRMS (ESI): m/z calc. for $\text{C}_{24}\text{H}_{20}\text{IO}_5\text{S}$ $[\text{M}+\text{H}]^+$: 547.0076, found: 547.0081.

(2*R*, 3*S*, 6*R*)-6-(5-Benzoyloxy)-1-hydroxy-6-iodo-7-(tosyloxy)naphthalene-2-yl)-2-methyltetrahydro-2*H*-pyran-3-yl acetate (443**)**

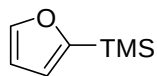


A solution of **234** (11 mg, 0.05 mmol) in dichloromethane (0.5 mL) was added dropwise to a suspension of **441** (55 mg, 0.10 mmol), hafnocene dichloride (28 mg, 0.075 mmol), silver perchlorate (31 mg, 0.15 mmol) and powdered 4Å molecular sieves (71 mg) in dichloromethane (1 mL) at -78°C . The resulting mixture was warmed to room temperature over 1 hour and stirred at this temperature for a further hour. After this time, the mixture was quenched with saturated aqueous sodium hydrogen carbonate (2 mL) and filtered through Celite (the filter cake washed with further dichloromethane). The organic phase was washed with water (5 mL), brine (5 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue chromatographed (3:1 hexanes/ethyl acetate) to yield the title product as an amorphous solid (20 mg, 58%); R_f : 0.55 (3:1 hexanes/ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz): δ 7.94 (s, Ar-*H*8, 1H), 7.87 (d, J = 8.4 Hz, 2H, $\text{OSO}_2\text{Ar-H}$), 7.70 (d, J = 8.4 Hz, 1H, Ar-*H*4), 7.64-7.61 (m, 2H, *H*-Ar- CH_2O), 7.47-7.28 (m, 2H, - $\text{OSO}_2\text{Ar-H}$ and 3H, *H*-Ar CH_2O , and 1H, Ar-*H*3), 5.67 (br. s, 1H, Ar-OH), 5.03 (m, 3H, PhCH_2O and Ar $\text{CH}(\text{O})\text{CH}_2$), 4.66-4.61 (m, 1H, CHOAc), 3.89-3.82 (m, 1H, H_3CCHO), 2.44 (s, 3H, Ar- CH_3), 2.18-2.12 (m, 2H, $\text{CH}(\text{OAc})\text{CH}_2\text{CH}_2$), 2.10 (s, 3H, CH_3CO), 2.07-2.01 (m, 2H, $\text{CH}(\text{OAc})\text{CH}_2\text{CH}_2$), 1.13 (d, J = 6.0 Hz, 3H, H_3CCHO); ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.29, 157.06, 152.54, 146.65, 145.53, 136.34, 133.11, 129.73, 128.93, 128.59, 128.42, 128.17, 128.07, 127.46, 126.35, 115.39, 111.24, 109.95, 95.05, 87.43, 75.79, 73.00, 67.80, 29.30, 24.05, 21.72, 21.16, 17.86; HRMS (ESI): m/z calc. for $\text{C}_{32}\text{H}_{31}\text{INaO}_8\text{S}$ [$\text{M}+\text{Na}$] $^+$: 725.0682, found: 725.0678.

2-(Furan-3-ylmethoxy)tetrahydro-2H-pyran (428)¹⁸⁴

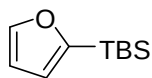


Para-toluenesulfonic acid (19 mg) was added to a solution of 3-furylmethanol (862 μ L, 10.0 mmol) and dihydropyran (4.5 mL, 50.0 mmol) in dichloromethane (40 mL), and the solution was stirred at room temperature for 2 hours. After this time, the solution was diluted with saturated aqueous sodium hydrogen carbonate solution (20 mL) and then water (20 mL), and the organic phase was separated, dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (6:1 hexanes/ethyl acetate) to obtain the title compound as a colourless oil (1.46 g, 80%); R_f : 0.68 (3:1 hexanes/ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 7.45 (m, 1H, $\text{CH}=\text{CHO}$), 7.42 (m, 1H, $\text{C}=\text{CHO}$), 6.45 (m, 1H, $\text{CH}=\text{CHO}$), 4.71 (t, $J = 3.6$ Hz, 1H, OCHO), 4.65 (d, $J = 12.0$ Hz, 1H, ArHCHO), 4.43 (d, $J = 12.0$ Hz, 1H, ArHCHO), 3.93 (m, 1H, CHOHCH), 3.56 (m, 1H, CHOHCH), 1.91-1.54 (m, 6H, CH_2); ^{13}C NMR (100 MHz, CDCl_3) δ 143.26, 140.76, 122.12, 110.50, 97.40, 62.20, 60.12, 30.54, 25.46, 19.41; MS (CI, NH_3) m/z : 200 $[\text{M} + \text{NH}_4]^+$.

Furan-2-yltrimethylsilane (432)¹⁸⁵

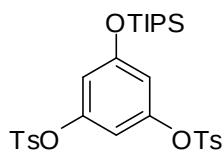
A solution of *n*-butyllithium (1.55 M in hexanes, 21.0 mL, 33.0 mmol) was added dropwise to a solution of furan (2.1 mL, 30.0 mmol) in THF (100 mL) at 0 °C. The solution was then warmed to room temperature and stirred for a further 4 hours. After this time, chlorotrimethylsilane (4.15 mL, 33 mmol) was added to the solution dropwise at 0 °C and stirred at room temperature for a further 10 hours, before slow addition of saturated aqueous ammonium chloride (20 mL). The mixture was diluted with water (50 mL) and extracted into diethyl ether (2 x 50 mL). The organic phase was dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was distilled (40 °C, <0.1 Torr) to give the title compound as a colourless oil (3.11 g, 74%); bp 106-110 °C (760 mmHg), lit.¹⁸⁵ 108-109 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.65 (d, *J* = 2.0 Hz, 1H, Ar-*H*5), 6.63 (d, *J* = 3.2 Hz, 1H, Ar-*H*3), 6.39 (dd, *J*₁ = 2.0 Hz, *J*₂ = 3.2 Hz, 1H, Ar-*H*4), 0.27 (s, 9H, -Si(CH₃)₃); ¹³C NMR (CDCl₃, 100 MHz) δ 146.50, 119.39, 109.28, 67.96, -1.64; MS (CI, NH₃): *m/z* 141 [M+H]⁺; HRMS (ESI): *m/z* calc. for C₇H₁₃OSi [M + H]⁺: 141.0736, found: 141.0730.

***tert*-Butyl(furan-2-yl)dimethylsilane (433)¹⁸⁶**



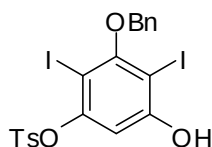
A solution of *n*-butyllithium (1.55 M in hexanes, 21.0 mL, 33.0 mmol) was added dropwise to a solution of furan (2.11 mL, 30.0 mmol) in THF (100 mL) at 0 °C. The solution was then warmed to room temperature and stirred for a further 4 hours. After this time, *tert*-butyl(chloro)dimethylsilane (4.97 g, 33.0 mmol) in THF (10 mL) was added dropwise to the solution at 0 °C and stirred at room temperature for a further 10 hours, before slow addition of saturated aqueous ammonium chloride (20 mL). The mixture was diluted with water (50 mL) and extracted into diethyl ether (2 x 50 mL). The organic phase was dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was distilled (70 °C, <0.1 Torr) to give the title compound as a colourless oil (3.95 g, 72%); ¹H NMR (CDCl₃, 400 MHz): δ 7.66 (d, *J* = 1.6 Hz, 1H, Ar-*H*5), 6.65 (d, *J* = 3.2 Hz, 1H, Ar-*H*3), 6.39 (dd *J*₁ = 1.6 Hz, *J*₂ = 3.2 Hz, 1H, Ar-*H*4), 0.93 (s, 9H, Si-C(CH₃)₃), 0.24 (s, 6H, -Si(CH₃)₂); ¹³C NMR (CDCl₃, 100 MHz): δ 146.61, 120.64, 109.17, 67.97, 26.30, 16.79, -6.31; MS (CI, NH₃): *m/z* 183 [M+H]⁺; HRMS (CI, NH₃) calc for C₁₀H₁₉OSi [M + H]⁺: 183.1205, found: 183.1206.

5-(Tri-*iso*-propylsilyloxy)-1,3-phenylene bis(4-methylbenzenesulfonate) (459)



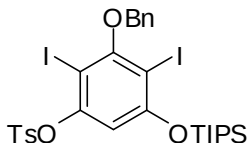
Chlorotri-*iso*-propylsilane (1.10 mL, 5.2 mmol) was added dropwise at 0 °C to a solution of phenol **384** (1.74 g, 4.0 mmol), imidazole (340 mg, 5.0 mmol) and DMAP (49 mg, 0.4 mmol) in dichloromethane (12 mL). The resulting solution was then warmed to room temperature and stirred for a further 3 hours, before being diluted with water (10 mL). The organic phase was washed with brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (9:1 hexanes/ethyl acetate) to deliver the title compound as a white, crystalline solid (2.03 g, 86%); R_f : 0.46 (9:1 hexanes/ethyl acetate); mp 69-70 °C (methanol /dichloromethane); IR: $\nu_{\max}$ 1618, 1597, 1586, 1458, 1357, 1345, 1188, 1088, 997, 976, 658; ^1H NMR (CDCl_3 , 400 MHz): δ 7.63 (d, J = 8.0 Hz, 4H, OSO_2ArH_o), 7.30 (d, J = 8.0 Hz, 4H, OSO_2ArH_m), 6.35 (s, 3H, Ar- H), 2.43 (s, 6H, Ar CH_3), 1.08-1.00 (m, 3H, $\text{OSiCH}(\text{CH}_3)_2$), 0.96 (d, 18H, J = 6.8 Hz, $\text{OSiCH}(\text{CH}_3)_2$); ^{13}C NMR (CDCl_3 , 100 MHz): δ 157.10, 150.15, 145.73, 131.90, 129.89, 128.49, 113.18, 109.92, 21.74, 17.68, 13.32; HRMS (ESI): m/z calc. for $\text{C}_{29}\text{H}_{39}\text{O}_7\text{S}_2\text{Si}$ $[\text{M}+\text{H}]^+$: 591.1907, found: 591.1898; Elem. Anal. calc for $\text{C}_{29}\text{H}_{38}\text{O}_7\text{S}_2\text{Si}$: C 58.95%, H 6.48%, found: C 59.03%, H 6.51%.

3-Benzyloxy-5-hydroxy-2,4-diiodophenyl 4-methylbenzenesulfonate (467)



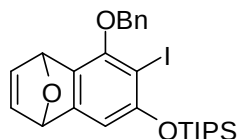
A solution of potassium hydroxide (1.36 g) in water (1 mL) and methanol (9 mL) was added dropwise to a solution of tosylate **437** (7.76 g) in dioxane (20 mL) and methanol (20 mL) and the resulting solution was stirred at room temperature for a further 18 hours. After this time, 1 M hydrochloric acid (25 mL) was added and the solution extracted into ethyl acetate (2 x 25 mL). The organic phase was washed with water (25 mL), brine (25 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (4:1 hexanes/ethyl acetate) to yield the title compound as a white, crystalline solid (5.04 g, 81%); R_f : 0.46 (2:1 hexanes/ethyl acetate); mp 86-87 °C (methanol); IR: $\nu_{\max}$ 3500, 1595, 1555, 1403, 1363, 1191, 1172, 1017, 748, 699; ^1H NMR (CDCl_3 , 400 MHz): δ 7.85 (d, J = 8.4 Hz, 2H, OSO_2ArH_o), 7.62-7.60 (m, 2H, HArCH_2O), 7.44-7.33 (m, 2H, HArCH_2O and 2H, OSO_2ArH_m), 6.96 (s, 1H, Ar- H), 5.90 (s, 1H, Ar-OH), 4.94 (s, 2H, PhCH_2O), 2.46 (s, 3H, ArCH_3); ^{13}C NMR (CDCl_3 , 100 MHz): δ 158.83, 156.93, 151.84, 146.01, 135.64, 132.49, 129.88, 128.87, 128.56, 128.48, 105.77, 81.97, 74.48, 21.78; HRMS (ESI): m/z calc. for $\text{C}_{20}\text{H}_{17}\text{I}_2\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$: 622.8886, found: 622.8912; Elem. Anal. calc. for $\text{C}_{20}\text{H}_{16}\text{I}_2\text{O}_5\text{S}$: C 38.61%, H 2.59%, S 5.15%, found: C 38.51%, H 2.58%, S 5.05%.

3-Benzyloxy-2,4-diiodo-5-(tri-iso-propylsilyloxy)phenyl 4-methylbenzene sulfonate (462)



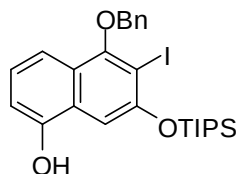
Chlorotri-iso-propylsilane (1.27 mL, 6.0 mmol) was added dropwise to a solution of phenol **467** (3.11 g, 5.0 mmol), imidazole (408 mg, 6.0 mmol) and DMAP (61 mg, 0.5 mmol) in dichloromethane (15 mL) at 0 °C. The resulting solution was then warmed to room temperature and stirred for a further 3 hours, before being diluted with water (15 mL). The organic phase was washed with brine, dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (100:1 to 8:1 hexanes/ethyl acetate) to deliver the title compound as a white, crystalline solid (3.39 g, 87%); R_f : 0.37 (9:1 hexanes/ethyl acetate); mp 74-75 °C (hexanes/ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz): δ 7.79 (d, J = 8.4 Hz, 2H, $\text{OSO}_2\text{Ar}H_o$), 7.64-7.62 (m, 2H, $H\text{ArCH}_2\text{O}$), 7.43-7.35 (m, 2H, $H\text{ArCH}_2\text{O}$), 7.32 (d, J = 8.4 Hz, 2H, $\text{OSO}_2\text{Ar}H_m$), 6.85 (s, 1H, Ar- H), 4.94 (s, 2H, PhCH_2O), 2.45 (s, 3H, Ar- CH_3), 1.33 (sep., 3H, J = 7.2 Hz, $\text{OSiCH}(\text{CH}_3)_2$), 1.15 (d, 18H, J = 7.2 Hz, $\text{OSiCH}(\text{CH}_3)_2$); ^{13}C NMR (CDCl_3 , 100 MHz): δ 159.41, 157.56, 151.30, 145.89, 136.00, 132.63, 129.85, 128.87, 128.54, 128.45, 108.56, 86.69, 74.16, 21.81, 18.06, 12.94; HRMS (ESI): m/z calc. for $\text{C}_{29}\text{H}_{37}\text{I}_2\text{O}_5\text{SSi}$ $[\text{M}+\text{H}]^+$: 779.0221, found: 779.0242; Elem. Anal. calc. for $\text{C}_{29}\text{H}_{36}\text{I}_2\text{O}_5\text{SSi}$: C 44.74%, H 4.66%, found: C 44.81%, H 4.59%.

(6-Benzyloxy-5-iodo-11-oxa-tricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5,9-tetraen-4-yloxy)-tri-iso-propyl-silane (469)



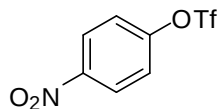
A solution of *iso*-propylmagnesium chloride (2.0 M in THF, 1.50 mL, 3.0 mmol) was added slowly to a solution of tosylate **462** (2.34 g, 3.0 mmol) and furan (1.66 mL, 24.0 mmol) in THF (12 mL) at -78°C , and the resulting solution was stirred at this temperature for a further 45 minutes. After this time, the solution was allowed to warm to room temperature and stirred for a further 16 hours. After this time, saturated aqueous ammonium chloride (10 mL) was added, and the mixture extracted into ethyl acetate (2 x 15 mL). The organic layer was washed with brine, dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (9:1 hexanes/ethyl acetate) to yield the title compound as a white, crystalline solid (1.40 g, 85%); mp $96-97^{\circ}\text{C}$ (hexanes/ethyl acetate); R_f : 0.30 (9:1 hexanes/ethyl acetate); IR: ν_{max} 2946, 2866, 1610, 1562, 1429, 1360, 1347, 1135, 878, 721; ^1H NMR (CDCl_3 , 400 MHz): δ 7.50-7.34 (m, 5H, $\text{HArCH}_2\text{O-}$), 6.91 (dd, $J_1 = 1.6$ Hz, $J_2 = 5.2$ Hz, 1H, $-\text{CH}=\text{CH-}$), 6.63 (dd, $J_1 = 1.6$ Hz, $J_2 = 5.2$ Hz, 1H, $-\text{CH}=\text{CH-}$), 6.60 (s, 1H, Ar-H), 5.78 (m, 1H, $-\text{CHOHC-}$), 5.59 (m, 1H, $-\text{CHOHC-}$), 5.12 (m, 2H, PhCH_2OAr), 1.35 (sep., $J = 7.6$ Hz, 3H, $\text{OSiCH}(\text{CH}_3)_2$), 1.15 (d, $J = 7.6$ Hz, 18H, $\text{OSiCH}(\text{CH}_3)_2$); ^{13}C NMR (CDCl_3 , 100 MHz): δ 154.92, 152.49, 151.64, 142.83, 142.05, 136.83, 129.09, 128.63, 128.22, 127.84, 107.80, 82.76, 82.36, 81.35, 74.87, 18.17, 13.26; MS (CI, NH_3): m/z 549 ($\text{M}+\text{H}$) $^+$; HRMS (CI, NH_3): m/z calc. for $\text{C}_{26}\text{H}_{33}\text{IO}_3\text{Si}$ [$\text{M}+\text{H}$] $^+$: 549.1322, found: 549.1320; Elem. Anal. calc for $\text{C}_{26}\text{H}_{33}\text{IO}_3\text{Si}$: C 56.93%, H 6.06%, found: C 57.04%, H 5.94%.

5-(Benzyloxy)-6-iodo-7-(triisopropylsilyloxy)naphthalen-1-ol (470)



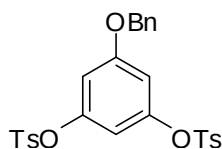
A solution of cycloadduct **469** (548 mg, 1.0 mmol) in dichloromethane (1.5 mL) was added slowly to *para*-toluenesulfonic acid (190 mg, 1.0 mmol) in dichloromethane (1.5 mL) and stirred at room temperature for a further 10 hours. After this time, the solution was diluted with saturated aqueous sodium bicarbonate (10 mL), the organic phase was washed with brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (9:1 hexanes/ethyl acetate) to give the title product as a pale brown amorphous solid (405 mg, 74%); R_f : 0.22 (9:1 hexanes/ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz): δ 7.70-7.68 (m, 2H, *H*-ArCH₂O-), 7.64 (d, J = 8.4 Hz, 1H, Ar-*H*4), 7.48-7.37 (m, 3H, *H*-ArCH₂O- and 1H, Ar-*H*8), 7.15 (t, J = 8.4 Hz, 1H, Ar-*H*3), 6.78 (d, J = 8.4 Hz, 1H, Ar-*H*2), 5.25 (s, 1H, Ar-OH), 5.09 (s, 2H, PhCH₂O-), 1.46 (sep., J = 7.2 Hz, 3H, OSiCH(CH₃)₂), 1.21 (d, J = 7.2 Hz, 18H, OSiCH(CH₃)₂); ^{13}C NMR (CDCl_3 , 100 MHz): δ 156.63, 152.58, 150.70, 138.99, 128.58, 128.24, 125.97, 125.29, 124.04, 115.03, 109.55, 103.86, 91.15, 75.40, 18.23, 13.11; MS (CI, NH₃): m/z 549 [M]⁺; HRMS (CI, NH₃): m/z calc. for C₂₆H₃₄IO₃Si [$\text{M} + \text{H}$]⁺: 549.1322, found: 549.1320; Elem. Anal. calc. for C₂₆H₃₃IO₃Si: C 56.93%, H 6.06%, found: C 57.04%, H 6.11%.

4-Nitrophenyl trifluoromethanesulfonate (505)



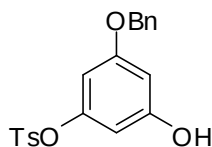
Triflic anhydride (9.3 mL, 55.0 mmol) was added dropwise to a solution of 4-nitrophenol (6.96 g, 50.0 mmol) in pyridine (12 mL, 150 mmol) and dichloromethane (100 mL) at 0 °C and the resulting solution was stirred at room temperature for a further 2 hours. After this time, water (100 mL) was added slowly, the organic phase was separated, washed with saturated aqueous copper (II) sulfate solution (2 x 50 mL), water (50 mL), brine (50 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting solid was recrystallised from hexane/ethyl acetate to give the title compound as a white, crystalline solid (13.28 g, 98%); R_f : 0.74 (2:1 hexanes/ethyl acetate); mp 51-53 °C, lit: 52-53 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 8.37 (m, 2H, Ar-*H*3 and Ar-*H*5), 7.48 (m, 2H, Ar-*H*2 and Ar-*H*6); ^{13}C NMR (CDCl_3 , 100 MHz): δ 153.10, 147.15, 125.99, 122.53, 118.65 (m, $J_{\text{C-F}} = 319$ Hz); MS (CI, NH_3): m/z : 297 $[\text{M}+\text{NH}_4]^+$.

5-Benzyloxy-1,3-phenylene bis(4-methylbenzenesulfonate) (462)



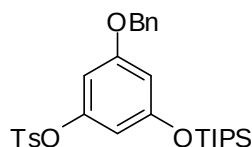
Benzyl bromide (1.78 mL, 15.0 mmol) was added slowly to a suspension of caesium carbonate (4.89 g, 15.0 mmol) and phenol **384** (4.34 g, 10.0 mmol) in THF (25 mL) and the solution was stirred at room temperature for 14 hours. After this time, water (25 mL) was added and the mixture was extracted into ethyl acetate (2 x 25 mL). The organic phase was separated, washed with brine (25 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (hexanes/ethyl acetate, 3:1) to deliver the title compound as a white, crystalline solid (4.51 g, 86%); R_f : 0.26 (3:1 hexanes/ethyl acetate); mp: 75-76 °C (hexanes/ethyl acetate); IR: $\nu_{\max}$; 2947, 2866, 1610, 1579, 1452, 1364, 1156, 1019, 861, 671; ^1H NMR (CDCl_3 , 400 MHz): δ 7.68 (d, J = 8.4 Hz, 4H, OSO_2ArH_o), 7.44-7.34 (m, 5H, $H\text{-ArCH}_2\text{O-}$ and 4H, $\text{OSO}_2\text{Ar-H}$), 6.60 (d, 2H, J = 2.4 Hz, Ar-H4 and Ar-H6), 6.28 (t, 1H, J = 2.4 Hz, Ar-H2), 4.92 (s, 2H, $\text{PhCH}_2\text{O-}$), 2.49 (s, 6H, Ar-CH_3); ^{13}C NMR (CDCl_3 , 100 MHz): δ 159.70, 150.32, 145.79, 135.55, 131.95, 129.94, 128.73, 128.47, 127.61, 109.28, 108.30, 70.63, 21.79; MS (CI, NH_3): m/z 548 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3): m/z calc. for $\text{C}_{27}\text{H}_{28}\text{NO}_7\text{S}_2$ $[\text{M} + \text{NH}_4]^+$: 542.1307, found: 542.1299; Elem. Anal. calc. for $\text{C}_{27}\text{H}_{24}\text{IO}_7\text{S}_2$: C 61.82%, H 4.61%, found: C 61.88%, H 4.57%.

3-Benzyloxy-5-hydroxyphenyl-4-methylbenzenesulfonate (463)



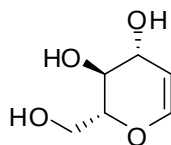
A solution of potassium hydroxide (136 mg) in water (0.1 mL) and methanol (0.9 mL) was added dropwise to a solution of tosylate **462** (525 mg) in dioxane (2.0 mL) and methanol (2.0 mL) and the resulting solution was stirred at room temperature for a further 8 hours. After this time, 1 M hydrochloric acid (2.5 mL) was added and the solution extracted into ethyl acetate (2 x 5 mL). The organic phase was washed with water (5 mL), brine (5 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (4:1 hexanes/ethyl acetate) to yield the title compound as a white, crystalline solid (258 mg, 70%); mp 70-71 °C (hexanes/ethyl acetate); R_f : 0.44 (2:1 hexanes/ethyl acetate); IR: $\nu_{\max}$ 3460, 2988, 2815, 1598, 1367, 1192, 1176, 1157, 1091, 991; ^1H NMR (CDCl_3 , 400 MHz): δ 7.72 (d, J = 8.4 Hz, 2H, OSO_2ArH_o), 7.40-7.30 (m, 5H, $H\text{-ArCH}_2\text{O}$ and 2H, OSO_2ArH_m), 6.35 (t, J = 2.4 Hz, 1H, Ar- H), 6.24 (t, J = 2.4 Hz, 1H, Ar- H), 6.14 (t, J = 2.4 Hz, 1H, Ar- H), 5.00 (br. s, 1H, Ar-OH), 4.92 (s, 2H, PhCH_2O), 2.44 (s, 3H, Ar- CH_3); ^{13}C NMR (CDCl_3 , 100 MHz): δ 160.27, 157.14, 150.92, 145.46, 136.19, 132.33, 129.82, 128.66, 128.52, 128.21, 127.54, 102.70, 101.69, 101.46, 70.31, 21.74; MS (CI, NH_3): m/z 388 $[\text{M}+\text{NH}_4]^+$; HRMS (CI, NH_3): m/z calc. for $\text{C}_{20}\text{H}_{18}\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$: 371.0953, found: 371.0946.

3-Benzyloxy-5-(tri-*iso*-propylsilyloxy)phenyl 4-methylbenzenesulfonate (464)



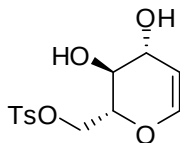
Chlorotri-*iso*-propylsilane (343 μ L, 1.6 mmol) was added dropwise to a solution of phenol **463** (502 mg, 1.4 mmol), imidazole (110 mg, 1.6 mmol) and DMAP (17 mg) in dichloromethane (4 mL) at 0 °C. The resulting solution was warmed to room temperature and stirred for a further 3 hours, before being diluted with water (10 mL). The organic phase was separated, washed with brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (100:1 to 8:1 hexanes/ethyl acetate) to deliver the title compound as a white, crystalline solid (604 mg, 85%); R_f : 0.65 (8:1 hexanes/ethyl acetate); mp 45-46 °C (hexanes/ethyl acetate); IR: 2944, 2866, 1608, 1580, 1453, 1365, 1158, 753, 660; ^1H NMR (CDCl_3 , 400 MHz): δ 7.70 (d, J = 8.4 Hz, 2H, OSO_2ArH_o), 7.40-7.31 (m, 5H, $H\text{-ArCH}_2\text{O-}$), 7.29 (d, J = 8.4 Hz, 2H, $-\text{OSO}_2\text{Ar-H}$, 2H), 6.35 (d, J = 2.4 Hz, 2H, Ar-H2 and Ar-H6), 6.02 (J = 2.0 Hz, 1H, Ar-H4), 4.94 (s, 2H, $\text{PhCH}_2\text{O-}$), 2.43 (s, 3H, Ar-CH_3), 1.12-1.08 (m, 3H, $\text{OSiCH}(\text{CH}_3)_2$), 0.99 (d, 18H, J = 6.8 Hz, $\text{OSiCH}(\text{CH}_3)_2$); ^{13}C NMR (CDCl_3 , 400 MHz): δ 159.93, 157.30, 150.79, 145.22, 136.35, 132.44, 129.71, 128.63, 128.59, 128.13, 127.49, 106.90, 106.11, 102.45, 70.27, 17.80, 12.47; MS (CI, NH_3): m/z 527 $[\text{M}]^+$, 544 $[\text{M}+\text{NH}_4]^+$; HRMS (CI, NH_3): m/z calc. for $\text{C}_{29}\text{H}_{39}\text{O}_5\text{SSi}$ $[\text{M}+\text{H}]^+$: 527.2287, found: 527.2285; Elem. Anal. calc. for $\text{C}_{29}\text{H}_{38}\text{O}_5\text{SSi}$: C 66.12%, H 7.27%, found: C 66.21%, H 7.33%.

(2*R*, 3*S*, 4*R*)-2-(Hydroxymethyl)-3,4-dihydro-2*H*-pyran-3,4-diol (420)¹⁶¹



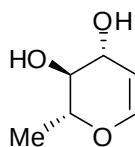
Potassium carbonate (1.04 g, 7.5 mmol) was added to a solution of triacetate **419** (40.84 g, 150 mmol) in methanol (170 mL) and the resulting solution was stirred at room temperature for 10 hours. After this time the solution was concentrated under reduced pressure and the resulting residue was either used with no further purification or chromatographed (ethyl acetate) to yield a white, crystalline solid (18.85 g, 86%); R_f : 0.05 (ethyl acetate); mp 58-60 °C (ethyl acetate), lit.¹⁶¹ 58-60 °C; ^1H NMR (D_2O , 400 MHz): δ 6.34 (dd, $J_1 = 6.0$ Hz, $J_2 = 1.6$ Hz, 1H, $\text{OCH}=\text{CH}$), 4.74 (dd, $J_1 = 6.0$ Hz, $J_2 = 1.6$ Hz, 1H, CHOH), 4.71 (br. s, 3H, OH), 4.16 (dt, $J_1 = 7.2$ Hz, $J_2 = 1.6$ Hz, 1H, CH_2CHO), 3.86-3.76 (m, 3H, $\text{OCH}=\text{CH}$ and CH_2OH), 3.61 (dd, $J_1 = 8.8$ Hz, $J_2 = 6.8$ Hz, 1H, CHOH); ^{13}C NMR (D_2O , 100 MHz): δ 143.75, 102.85, 78.17, 68.84, 68.32, 60.09; MS (CI, NH_3): m/z 164 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3): m/z calc. for $\text{C}_6\text{H}_{14}\text{NO}_4$ $[\text{M} + \text{NH}_4]^+$: 164.0923, found: 164.0920.

((2*R*, 3*S*, 4*R*)-3,4-Dihydroxy-3,4-dihydro-2*H*-pyran-2-yl)methyl 4-methylbenzene sulfonate (421)¹⁶⁰



Tosyl chloride (8.58 g, 45.0 mmol) was added portionwise to a solution of triol **420** (4.38 g, 30.0 mmol) in pyridine (40 mL) and dichloromethane (40 mL) at 0 °C. The solution was warmed to room temperature and stirred for a further 3 hours. After this time, the solution was re-cooled to 0 °C and water (20 mL) was added slowly. After a further five minutes, the mixture was diluted with water (40 mL) and dichloromethane (20 mL). The organic phase was separated, washed with saturated aqueous copper (II) sulfate solution (3 x 40 mL), water (2 x 100 mL), brine (50 mL), dried over magnesium sulfate and concentrated under reduced pressure to give the title compound as the major component of the residue, as a pale yellow oil (7.39 g, 82%), which was used in subsequent reactions without further purification; R_f : 0.53 (ethyl acetate); ^1H NMR (CDCl_3 , 400 MHz): δ 7.81 ($J = 8.0$ Hz, 2H, OSO_2ArH), 7.35 (d, $J = 8.0$ Hz, 2H, OSO_2ArH), 6.23 (dd, $J_1 = 6.0$ Hz, $J_2 = 1.6$ Hz, 1H, $\text{OCH}=\text{CH}$), 4.75 (dd, $J_1 = 6.0$ Hz, $J_2 = 1.6$ Hz, 1H, CHOH), 4.46 (dd, $J_1 = 11.2$ Hz, $J_2 = 4.0$ Hz, 1H, CHOH), 4.30-4.25 (m, 2H, $\text{OCH}=\text{CH}$ and TsOCH_2), 3.91 (ddd, $J_1 = 10$ Hz, $J_2 = 3.8$ Hz, $J_3 = 2.0$ Hz, 1H, TsOCH_2CHO), 3.75 (dd, $J_1 = 10$ Hz, $J_2 = 7.6$ Hz, 1H, TsOCH_2), 2.45 (s, 3H, Ar-CH_3); ^{13}C NMR (CDCl_3 , 100 MHz): δ 145.21, 143.95, 132.53, 129.96, 128.04, 103.12, 75.63, 69.57, 69.23, 68.05, 21.65; MS (CI, NH_3): m/z 300 $[\text{M}]^+$.

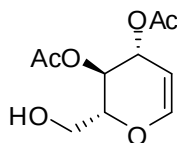
(2R, 3S, 4R)-2-Methyl-3,4-dihydro-2H-pyran-3,4-diol (424)¹⁶⁰



A solution of lithium aluminium hydride (2.0 M in THF, 128 mL, 256 mmol) was added dropwise to a solution of tosylate **421** (25.59 g, 85.2 mmol) in THF (345 mL) at 0 °C. The resulting mixture was then heated under reflux for a further 1.5 hours, before being re-cooled to 0 °C, whereupon water (9.6 mL) was added very slowly, followed by 20% aqueous sodium hydroxide (9.6 mL) and water (28.8 mL). The mixture was then diluted with diethyl ether (300 mL), filtered through Celite (with additional washing of filter cake with warm diethyl ether), and the organic phase was separated, washed with brine (2 x 200 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue chromatographed (ethyl acetate) to yield the title product as a white, crystalline solid (5.32 g, 48%).

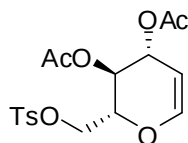
Alternatively, potassium carbonate (101 mg) was added to a solution of diacetate **231** (3.90 g, 18.2 mmol) in methanol (22 mL) and the resulting mixture stirred at room temperature for a further 12 hours. After this time, the mixture was concentrated under reduced pressure and the resulting residue was chromatographed (ethyl acetate) to yield the title product as a white crystalline solid (2.18 g, 92%); R_f : 0.28 (ethyl acetate); mp 71-73 °C (hexanes/ethyl acetate), lit.¹⁶⁰ 72-73 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 6.30 (dd, $J_1 = 6.0$ Hz, $J_2 = 1.6$ Hz, 1H, $\text{OCH}=\text{CH}$), 4.69 (dd, $J_1 = 6.0$ Hz, $J_2 = 2.0$ Hz, 1H, CHOH), 4.20 (dt, $J_1 = 7.6$ Hz, $J_2 = 2.0$ Hz, 1H, CHOH), 3.88-3.80 (m, 1H, $\text{OCH}=\text{CH}$), 3.66 (br. s, 1H, CH-OH), 3.40 (dd, $J_1 = 10$ Hz, $J_2 = 7.6$ Hz, 1H, H_3CCHO), 3.26 (br. s, CH-OH , 1H), 1.37 (d, $J = 6.4$ Hz, 3H, CHOCH_3); ^{13}C NMR (CDCl_3 , 100 MHz): δ 144.60, 103.11, 75.00, 74.73, 69.97, 17.28; MS (CI, NH_3): m/z 130 $[\text{M}]^+$, 148 $[\text{M}+\text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_6\text{H}_{14}\text{NO}_3$ $[\text{M} + \text{NH}_4]^+$: 148.0974, found: 148.0973.

(2*R*, 3*S*, 4*R*)-2-(Hydroxymethyl)-3,4-dihydro-2*H*-pyran-3,4-diyl diacetate (422**)**¹⁶¹



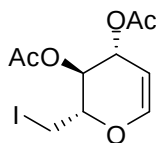
CCL lipase (2.21 g) was added to a solution of glucal **419** (6.81 g) in acetone (25 mL), di-iso-propyl ether (42 mL) and pH 7 phosphate buffer (255 mL) and the resulting mixture was stirred at room temperature for 18 hours. After this time, the solution was filtered through Celite and extracted into ethyl acetate (2 x 100 mL). The organic phase was washed with brine (2 x 100 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (1:1 hexanes/ethyl acetate) to yield the title compound (4.49 g, 78%) as a colourless oil; R_f : 0.45 (1:1 hexanes/ethyl acetate); $[\alpha]_D$: (c 1.0, chloroform) -55.1 , lit:¹⁶¹ (c 1.0, chloroform) -55.5); ^1H NMR (400 MHz, CDCl_3) δ 6.46 (d, $J = 6.0$ Hz, 1H, -CH=CHO-), 5.43 (m, 1H, CHOAc), 5.20 (m, 1H, CHOAc), 4.79 (m, $J_1 = 6.0$ Hz, $J_2 = 2.8$ Hz, 1H, -CH=CHO), 4.01 (m, 1H, OCHCH₂OH), 3.74 (qd, $J_1 = 12.7$ Hz, $J_2 = 3.7$ Hz, 2H, CH₂OH), 2.33 (br.s, 1H, -CH₂OH), 2.10 (s, 3H, CH₃CO-), 2.04 (s, 3H, CH₃CO-); ^{13}C NMR (100 MHz, CDCl_3) δ 170.62, 145.81, 99.12, 76.61, 68.37, 67.79, 60.60, 21.06, 20.85; MS (CI, NH₃) m/z : 248 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH₃) m/z calc. for C₁₀H₁₈NO₆ $[\text{M} + \text{NH}_4]^+$: 248.1134, found: 248.1129; Elem. Anal. calc. for C₁₀H₁₄O₆: C 52.17%, H 6.13%, found: C 52.20%, H 6.04%.

(2R, 3S, 4R)-2-(tosyloxymethyl)-3,4-dihydro-2H-pyran-3,4-diyl diacetate (423)¹⁶¹



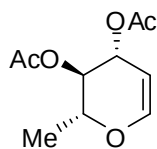
A solution of tosyl chloride (17.16 g, 90.0 mmol) in dichloromethane (70 mL) was added slowly to a solution of **420** (13.81 g) in pyridine (48 mL), at 0 °C. The solution was warmed to room temperature and stirred for 16 hours, before being quenched slowly with water (10 mL) at 0 °C. The mixture was further diluted with water (50 mL) and the organic phase was washed with saturated aqueous copper (II) sulfate solution (3 x 50 mL), water (50 mL), brine (50 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (2:1 hexanes/ethyl acetate) to yield the title compound as a white solid (16.59 g, 72%); mp 106-107 °C (dichloromethane/methanol), lit.¹⁶¹ 106-108 °C; R_f : 0.42 (dichloromethane); $[\alpha]_D$: (c 1.0, chloroform) +14.0 (lit.¹⁶¹ (c 1.2, chloroform) +14.0); ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, J = 8.3 Hz, 2H, OSO₂Ar-*H*), 7.38 (d, 8.3 Hz, 2H, OSO₂Ar-*H*), 6.37 (dd, 1H, J_1 = 6.2 Hz, J_2 = 1.1 Hz, -CH=CH-O-), 5.26 (t, 1H, J = 4.7 Hz, CHOAc), 5.12 (m, 1H, CHOAc), 4.81 (m, 1H, -CH=CH-O-), 4.26-4.18 (m, 3H, -CH₂OTs and -OCHCH₂OTs), 2.44 (s, 3H, Ar-CH₃), 2.03 (s, 3H, O₂CCH₃), 2.02 (s, 3H, O₂CCH₃); ¹³C NMR (100 MHz, CDCl₃) δ 170.25, 169.43, 145.32, 132.60, 130.04, 129.90, 128.08, 98.96, 73.24, 67.01, 66.63, 66.44, 21.68, 20.96, 20.74; MS (CI, NH₃) m/z : 402 [M + NH₄]⁺; HRMS (CI, NH₃) m/z calc. for C₁₇H₂₄NO₈S [M + NH₄]⁺: 402.1223, found: 402.1223; Elem. Anal. calc. for C₁₇H₂₀O₈S: C 53.12%, H 5.24%, S 8.34%, found: C 53.07%, H 5.15%, S 8.27%.

(2*S*, 3*S*, 4*R*)-2-(Iodomethyl)-3,4-dihydro-2*H*-pyran-3,4-diyl diacetate (425**)**¹⁸⁷



Sodium iodide (8.99 g, 60.0 mmol) was added to a solution of **423** (7.69 g, 20.0 mmol) in methyl *iso*-butyl ketone (130 mL) and the resulting mixture was heated under reflux for 16 hours. After this time, the mixture was cooled, filtered, concentrated under reduced pressure and the resulting residue was chromatographed (4:1 hexanes/ethyl acetate) to give the title compound (6.21 g, 91%) as a colourless oil; R_f : 0.42 (4:1 hexanes/ethyl acetate); $[\alpha]_D$: -32.8 (c 1.2, chloroform, lit.¹⁸⁷ -37 , c 1.2, chloroform); ^1H NMR (400 MHz, CDCl_3) δ 6.48 (d, $J = 6.1$ Hz, 1H, $\text{CH}=\text{CH}-\text{O}-$), 5.29 (m, 1H, CHOAc), 5.25 (m, 1H, CHOAc), 4.85 (q, $J_1 = 6.0$ Hz, $J_2 = 3.3$ Hz, 1H, $\text{CH}=\text{CH}-\text{O}$), 4.10 (*app.* q, 1H, CHCH_2I), 3.44-3.32 (m, 2H, $-\text{CH}_2\text{I}$), 2.09 (s, 3H, O_2CCH_3), 2.05 (s, 3H, O_2CCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ 170.29, 169.48, 145.43, 98.89, 74.88, 69.82, 66.68, 21.03, 20.88, 1.86; MS: 356 $[\text{M}+\text{NH}_4]^+$; Elem. Anal. calc. for $\text{C}_{10}\text{H}_{13}\text{IO}_5$: C 35.31%, H 3.85%, found: C 35.34%, H 3.77%.

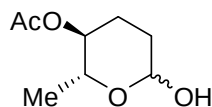
(2R, 3S, 4R)-2-Methyl-3,4-dihydro-2H-pyran-3,4-diyl diacetate (231)



ABCN (21 mg) was added to a solution of **425** (6.12 g, 18.0 mmol) and tributyltin hydride (7.26 mL, 27.0 mmol) in toluene (85 mL) at 60 °C, and the resulting solution was heated under reflux for 2 hours. After this time, the solution was cooled, concentrated under reduced pressure and the resulting residue redissolved in diethyl ether (50 mL), and vigorously stirred with a 10% aqueous potassium fluoride solution (25 mL) for 45 minutes, filtered and the organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was passed through a short plug of 10% KF in silica and then chromatographed (1:0 to 4:1 hexanes/ethyl acetate) to obtain the title compound as a colourless oil (3.77 g, 98%).

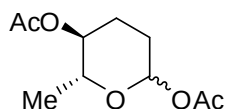
Alternatively, acetic anhydride (18.9 mL, 200 mmol) was added slowly to a solution of **424** (4.35 g, 33.4 mmol) in dichloromethane (26 mL) and pyridine (26 mL) at 0 °C. The resulting mixture was stirred at room temperature for 16 hours, after which time water (40 mL) was added, and the organic phase was washed with saturated aqueous copper (II) sulfate solution (4 x 50 mL), water (2 x 50 mL), brine, (50 mL) dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was then chromatographed (4:1 hexanes/ethyl acetate) to yield the title compound as a colourless oil (6.14 g, 86%); R_f : 0.58 (3:1 hexanes/ethyl acetate); $[\alpha]_D -60.8$ (c 1.0, chloroform); ^1H NMR (400 MHz, CDCl_3) δ 6.41 (d, J = 6.0 Hz, 1H, $\text{OCH}=\text{CH}$), 5.33 (m, 1H, $\text{CH}=\text{CHCHOAc}$), 5.01 (dd, J_1 = 8.4 Hz, J_2 = 6.0 Hz, 1H, CHOAc), 4.76 (dd, J_1 = 6.0 Hz, J_2 = 3.2 Hz, 1H, $\text{OCH}=\text{CH}$), 4.10 (m, 1H, H_3CCHO), 2.07 (s, 3H, COCH_3), 2.03 (s, 3H, COCH_3), 1.30 (d, J = 6.4 Hz, 3H, $\text{H}_3\text{CHCO-}$), ^{13}C NMR (100 MHz, CDCl_3) δ 170.65, 169.91, 145.98, 98.78, 72.52, 71.83, 68.30, 21.09, 20.90, 16.56; MS (CI, NH_3) m/z : 232 $[\text{M} + \text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{10}\text{H}_{18}\text{NO}_5$ $[\text{M} + \text{NH}_4]^+$: 232.1185, found 232.1187.

(2R,3S)-6-hydroxy-2-methyltetrahydro-2H-pyran-3-yl acetate (236)¹³²



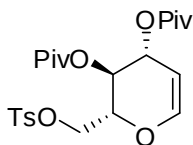
A solution of **231** (2.14g, 10.0 mmol) in water (40 mL) was heated at 80 °C for 3 hours. After this time, the solution was extracted with ethyl acetate (2 x 30 mL) and the organic phase was dried over magnesium sulfate and concentrated under reduced pressure. A solution of the resulting residue, chiefly consisting of aldehyde **235**, in ethanol (20 mL) was added to a suspension of Pd/C in degassed ethanol (130 mL) under a hydrogen atmosphere. The resulting mixture was stirred at room temperature for 18 hours, after which time the mixture was filtered through Celite and concentrated under reduced pressure. The resulting residue was chromatographed (3:2 diethyl ether/hexanes) to obtain the title compound as a colourless oil (1.24 g, 71%) in an inseparable 1:1 mixture of anomers; R_f : 0.42 (3:2 diethyl ether/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 5.22 (s, 1H, α -anomer OCHOH), 4.79 (dd, $J_1 = 9.2$ Hz, $J_2 = 2.0$ Hz, 1H, β -anomer OCHOH), 4.50-4.40 (m, 2H, α - and β -anomer CHOAc), 4.03 (m, 1H, α - or β -anomer H_3CHCO), 3.67 (br. s, 1H, α - or β -anomer CHOH), 3.55 (m, 1H, α - or β -anomer H_3CHCO), 3.16 (br. s, 1H, α - or β -anomer CHOH), 2.14 (m, 1H, CH_2), 2.04 (s, 3H, α - or β -anomer CH_3CO), 2.03 (s, 3H, α - or β -anomer CH_3CO), 1.99-1.76 (m, 6H, α - and β -anomer CH_2), 1.62-1.41 (m, 2H, α - and β -anomer CH_2), 1.20 (d, $J = 6.4$ Hz, 3H, α - or β -anomer, H_3CHCO), 1.13 (d, $J = 6.4$ Hz, 3H, α - or β -anomer, H_3CHCO); ^{13}C NMR (100 MHz, CDCl_3) δ 170.42, 170.35, 95.81, 90.81, 73.50, 73.48, 72.71, 68.11, 67.94, 66.67, 63.55, 31.70, 29.17, 27.38, 23.36, 21.19, 21.14, 18.07, 17.88; MS (CI, NH_3) m/z : 174 $[\text{M}]^+$; 157 $[\text{M}-\text{OH}]^+$, 192 $[\text{M}+\text{NH}_4]^+$, 348 $[\text{M}]^{2+}$; HRMS (CI, NH_3) m/z calc. for $\text{C}_8\text{H}_{18}\text{NO}_4$ $[\text{M} + \text{NH}_4]^+$: 192.1236, found: 192.1242.

(5*S*, 6*R*)-6-Methyltetrahydro-2*H*-pyran-2,5-diyl diacetate (234)



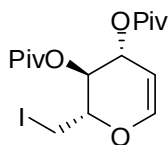
Acetic anhydride (5.2 mL, 85.4 mmol) was added slowly to a solution of hemiacetal **236** (1.21 g, 6.9 mmol) in pyridine (1.1 mL, 13.8 mmol) and dichloromethane (7 mL) at 0 °C, before being warmed to room temperature and stirred for a further 14 hours. After this time, saturated aqueous sodium hydrogen carbonate (5 mL), was added slowly, followed by water (10 mL). The organic phase was washed with saturated aqueous copper (II) sulfate solution (2 x 10 mL), water (10 mL), brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (2:1 hexanes/ethyl acetate) to yield the title product as a colourless oil (1.26 g, 84%) and as a 1 : 2 (α : β) mixture of anomers; R_f : 0.50 (3:2 diethyl ether/hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 6.06 (t, J = 2.4 Hz, 1H, α -anomer OCHOAc), 5.72 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H, β -anomer OCHOAc), 4.55-4.41 (m, 2H, α - and β -anomer H_3CCHO), 3.91-3.83 (m, 1H, α -anomer CHOAc), 3.69-3.62 (m, 1H, β -anomer CHOAc), 2.10 (s, 6H, α - and β -anomer CH_3CO), 2.07 (s, 6H, α - and β -anomer CH_3CO), 2.05-1.41 (m, 8H, α - and β -anomer CH_2CH_2), 1.23 (d, J = 6.0 Hz, 3H, β -anomer H_3CCHO), 1.17 (d, J = 6.0 Hz, 3H, α -anomer H_3CCHO); ^{13}C NMR (CDCl_3 , 100 MHz): δ 170.17, 170.04, 169.50, 169.29, 93.47, 90.80, 74.00, 72.71, 71.97, 68.84, 28.40, 27.92, 26.32, 23.69, 21.05, 18.07, 17.81; MS (CI, NH_3): m/z 234 [$\text{M}+\text{NH}_4$] $^+$; HRMS (CI, NH_3): m/z calc. for $\text{C}_{10}\text{H}_{20}\text{NO}_5$ [$\text{M}+\text{NH}_4$] $^+$: 234.1341, found: 234.1339.

(2*R*, 3*S*, 4*R*)-2-(Tosyloxymethyl)-3,4-dihydro-2*H*-pyran-3,4-diyl bis(2,2-dimethylpropanoate) (446)



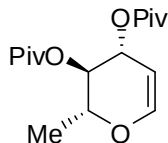
Tosyl chloride (2.85 g, 15.0 mmol) was added portionwise to a solution of triol **420** (1.46 g, 10.0 mmol) in pyridine (13 mL) and dichloromethane (13 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for a further 8 hours. After this time, the solution was re-cooled to 0 °C and DMAP (122 mg, 1.0 mmol) in dichloromethane (1 mL) was added, followed by slow addition of pivaloyl chloride (7.4 mL, 60.0 mmol). The resulting solution was warmed to room temperature and stirred for a further 14 hours. After this time, saturated aqueous sodium hydrogen carbonate (15 mL) was added slowly. The organic phase was separated, washed with saturated aqueous copper (II) sulfate solution (2 x 20 mL), water (20 mL), brine (20 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (9:1 hexanes/ethyl acetate) to yield the title product as a white, crystalline solid (3.56 g, 76%); R_f : 0.45 (9:1 hexanes/ethyl acetate); mp 43-45 °C (hexanes/ethyl acetate); IR: $\nu_{\max}$ 2975, 2874, 1737, 1649, 1364, 1177, 1148, 1115, 930. 674; ^1H NMR (CDCl_3 , 400 MHz): δ 7.78 (d, J = 8.0 Hz, 2H, $\text{OSO}_2\text{Ar-H}$), 7.34 (d, J = 8.0 Hz, 2H, $\text{OSO}_2\text{Ar-H}$), 6.32 (dd, J_1 = 6.0 Hz, J_2 = 1.2 Hz, 1H, OCH=CH), 5.22 (t, J = 4.4 Hz, 1H, CHOPiv), 5.10 (dd, J_1 = 7.2 Hz, J_2 = 5.6 Hz, 1H, CHOPiv), 4.78 (dd, J_1 = 6.4 Hz, J_2 = 3.6 Hz, 1H, OCH=CH), 4.28-4.08 (m, 3H, CH_2OTs and OCHCH_2OTs), 2.44 (s, 3H, Ar-CH_3), 1.14 (s, 18H, $\text{COC}(\text{CH}_3)_3$); ^{13}C NMR (CDCl_3 , 100 MHz): δ 171.49, 176.61, 145.07, 132.56, 129.85, 128.06, 99.01, 73.45, 66.87, 66.60, 66.48, 38.70, 26.97, 26.86, 21.61; MS (CI, NH_3): m/z 486 $[\text{M}+\text{NH}_4]^+$; HRMS (CI, NH_3): m/z calc. for $\text{C}_{23}\text{H}_{36}\text{NO}_8\text{S}$ $[\text{M}+\text{NH}_4]^+$: 486.21.62, found: 486.2153; Elem. Anal. calc. for $\text{C}_{23}\text{H}_{32}\text{O}_8\text{S}$: C 58.96%, H 6.88%, found: C 59.04%, H 6.93%.

(2*S*, 3*S*, 4*R*)-2-(Iodomethyl)-3,4-dihydro-2*H*-pyran-3,4-diyl bis(2,2-dimethylpropanoate) (447)



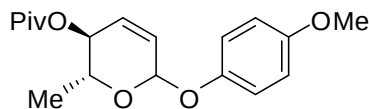
A suspension of tosylate **446** (2.12 g, 4.5 mmol) and sodium iodide (2.03 g, 13.6 mmol) in methyl *iso*-butyl ketone (30 mL) was heated under reflux for 6 hours, after which time the mixture was cooled, filtered, concentrated under reduced pressure and the resulting residue was chromatographed (9:1 hexanes/ethyl acetate) to deliver the title compound as a white, crystalline solid (1.68 g, 88 %); R_f : 0.52 (9:1 hexanes/ethyl acetate); mp 92-93 °C (hexanes/ethyl acetate); IR: $\nu_{\max}$ 2973, 2871, 1731, 1657, 1479, 1277, 1237, 1145, 1061, 998; ^1H NMR (CDCl_3 , 400 MHz): δ 6.47 (dd, $J_1 = 6.1$ Hz, $J_2 = 1.0$ Hz, 1H, $\text{OCH}=\text{CH}$), 5.29-5.24 (m, 2H, CHOPiv and CHOPiv), 4.83 (dd, $J_1 = 6.1$ Hz, $J_2 = 3.2$ Hz, 1H, $\text{OCH}=\text{CH}$), 4.08 (*app.* dq, $J_1 = 11.7$ Hz, $J_2 = 6.61$ Hz, $J_3 = 1.0$ Hz, 1H, OCHCH_2I), 3.35 (ddd, $J_1 = 17.8$ Hz, $J_2 = 10.8$ Hz, $J_3 = 5.9$ Hz, 2H, CH_2I), 1.19 (s, 9H, $\text{COC}(\text{CH}_3)_3$), 1.18 (s, 9H, $\text{COC}(\text{CH}_3)_3$); ^{13}C NMR (CDCl_3 , 100 MHz): δ 177.69, 176.67, 145.25, 99.24, 75.05, 69.51, 67.02, 38.73, 27.04, 1.91; MS (CI, NH_3): m/z 442 $[\text{M}+\text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{16}\text{H}_{29}\text{INO}_5$ $[\text{M}+\text{NH}_4]^+$: 442.1091, found 442.1099; Elem. Anal. calc. for $\text{C}_{16}\text{H}_{25}\text{IO}_5$: C 45.29%, H 5.94%, found: C 45.27%, H 5.84%.

(2*R*, 3*R*, 4*R*)-2-Methyl-3,4-dihydro-2*H*-pyran-3,4-diyl bis(2,2-dimethylpropanoate) (448)



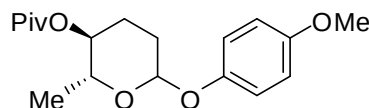
A solution of iodide **447** (1.14 g, 2.7 mmol) and tri-*n*-butyltin hydride (940 μ L, 3.5 mmol) in toluene (12 mL) was heated to 60 $^{\circ}$ C, whereupon ABCN (66 mg, 0.26 mmol) was added and the resulting mixture was heated under reflux for a further 2 hours. After this time, the solution was concentrated under reduced pressure and the resulting residue was taken up in diethyl ether (10 mL) and stirred vigorously with 10% aqueous potassium fluoride (5 mL) for 30 minutes. After this time, the mixture was filtered through Celite, the organic phase was separated, washed with water (10 mL), brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue chromatographed (hexanes/ethyl acetate 1:0 to 9:1) to deliver the title compound as a white, crystalline solid (714 mg, 89%); R_f : 0.55 (hexanes/ethyl acetate 9:1); mp 43-45 $^{\circ}$ C (hexanes/ethyl acetate); IR: $\nu_{\max}$ 2970, 2874, 1739, 1717, 1649, 1481, 1280, 1236, 1156, 1134, 1112, 1042, 749; ^1H NMR (CDCl_3 , 400 MHz): δ 6.41 (dd, $J_1 = 6.2$ Hz, $J_2 = 1.4$ Hz, 1H, $\text{OCH}=\text{CH}$), 5.34 (ddd, $J_1 = 6.6$ Hz, $J_2 = 2.7$ Hz, $J_3 = 1.4$ Hz, 1H, CHOPiv), 5.07 (dd, $J_1 = 8.7$ Hz, $J_2 = 6.6$ Hz, 1H, CHOPiv), 4.74 (dd, $J_1 = 6.2$ Hz, $J_2 = 2.7$ Hz, 1H, $\text{OCH}=\text{CH}$), 4.14-4.07 (m, 1H, H_3CCHO), 1.29 (d, 3H, $J = 6.6$ Hz, H_3CCHO), 1.19 (s, 9H, $\text{COC}(\text{CH}_3)_3$), 1.16 (s, 9H, $\text{COC}(\text{CH}_3)_3$); ^{13}C NMR (CDCl_3 , 100 MHz): δ 178.01, 177.08, 145.84, 99.16, 72.68, 71.29, 68.41, 38.74, 38.70, 27.04, 16.57; MS (CI, NH_3): m/z 316 $[\text{M}+\text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{16}\text{H}_{30}\text{NO}_5$ $[\text{M}+\text{NH}_4]^+$: 316.2124, found: 316.2134.

(2R, 3S)-6-(4-Methoxyphenoxy)-2-methyl-3,6-dihydro-2H-pyran-3-yl pivalate
(455)



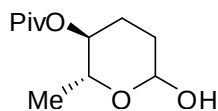
A solution of DTAD (3.68 g, 16.0 mmol) in dichloromethane (5 mL) was added slowly to a solution of diol **424** (1.30 g, 10.0 mmol), triphenylphosphine (2.89 g, 11.0 mmol) and phenol **148** (1.49 g, 12.0 mmol) in dichloromethane (15 mL) at 0 °C. The resulting mixture was allowed to warm to room temperature over the course of 1.5 hours, after which time the solution was concentrated under reduced pressure and the resulting residue was chromatographed (hexanes/ethyl acetate 2:1) in order to obtain the partially pure alcohol **454**, along with the co-eluting hydrazine derived from DTAD (Σ = 1.72 g). This mixture and DMAP (89 mg, 0.73 mmol) were then dissolved in pyridine (1.2 mL, 14.6 mmol) and dichloromethane (15 mL) and cooled to 0 °C, whereupon pivaloyl chloride (2.7 mL, 21.8 mmol) was added slowly. The resulting solution was warmed to room temperature and stirred for a further 14 hours. After this time, water (20 mL) was added, and the organic phase was separated, washed with saturated aqueous copper (II) sulfate solution (2 x 20 mL), water (20 mL), brine (20 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (9:1 hexanes/ethyl acetate) in order to obtain the title product as white, crystalline solid as a 9:1 (α : β) mixture of anomers (1.54 g, 48% over two steps); R_f : 0.44 (9:1 hexanes/ethyl acetate); mp: 42-43 °C (hexanes/ethyl acetate); IR: $\nu_{\max}$ 2934, 2874, 1727, 1507, 1216, 1151, 1094, 1038, 994, 960, 826, 762; ^1H NMR (CDCl_3 , 400 MHz): (for α anomer) δ 7.04 (m, 2H, Ar-*H*), 6.84 (m, 2H, Ar-*H*), 5.95 (m, 2H, CH=CH), 5.54 (m, 1H, OCHOAr), 5.10 (app. d, J = 9.4 Hz, 1H, CHOPiv), 4.14 (dq, J_1 = 9.4 Hz, J_2 = 6.2 Hz, 1H, H_3CCHO), 3.78 (s, 3H, Ar-OCH₃), 1.22-1.20 (m, 9H, $\text{COC}(\text{CH}_3)_3$ and 3H, H_3CCHO); ^{13}C NMR (CDCl_3 , 100 MHz): δ 177.94, 154.97, 151.40, 130.84, 126.92, 118.29, 114.56, 94.10, 70.25, 65.72, 55.65, 38.83, 27.03, 17.90; MS (CI, NH_3): m/z 338 [$\text{M}+\text{NH}_4$]⁺; HRMS (CI, NH_3) m/z calc. for $\text{C}_{18}\text{H}_{28}\text{NO}_5$ [$\text{M}+\text{NH}_4$]⁺: 338.1967, found: 338.1969.

(2*R*, 3*S*)-6-(4-Methoxyphenoxy)-2-methyltetrahydro -2*H*-pyran-3-yl pivalate
(456)



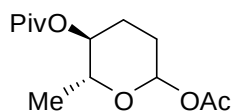
10% Pd/C (159 mg) was added to a solution of alkene **455** (760 mg, 2.4 mmol) in degassed methanol (16 mL) and the resulting mixture was stirred under a hydrogen atmosphere for 12 hours. After this time, the mixture was filtered through Celite, concentrated under reduced pressure and the resulting residue was chromatographed (9:1 hexanes/ethyl acetate) to deliver the title product as a white, crystalline solid (630 mg, 82%) as a 9:1 (α : β) mixture of anomers; R_f : 0.42 (9:1 hexanes/ethyl acetate); mp 34-35 °C (hexanes/ethyl acetate); IR: 2974, 2832, 1717, 1503, 1212, 1202, 1151, 1099, 1008, 957, 830; ^1H NMR (CDCl_3 , 400 MHz): (for α anomer) δ 7.02 (m, 2H, Ar-*H*), 6.83 (m, 2H, Ar-*H*), 5.38 (m, 1H, OCHOAr), 4.56-4.50 (m, 1H, H_3CCHO), 3.98-3.91 (m, 1H, CHOPiv), 3.77 (s, 3H, Ar-OCH₃), 2.05-1.93 (m, 4H, CH_2CH_2), 1.19 (m, 9H, $\text{COC}(\text{CH}_3)_3$), 1.11 (d, 3H, J = 6.4 Hz, H_3CCHO); ^{13}C NMR (CDCl_3 , 100 MHz): δ 177.64, 154.60, 150.92, 122.18, 117.66, 114.53, 114.37, 95.58, 75.85, 73.26, 72.92, 67.66, 67.30, 55.63, 38.73, 29.32, 29.18, 27.05, 25.29, 23.81, 18.19, 17.86; MS (CI, NH_3): m/z 340 $[\text{M}+\text{NH}_4]^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{18}\text{H}_{30}\text{NO}_5$ $[\text{M}+\text{NH}_4]^+$: 340.2124, found: 340.2132; Elem. Anal. calc. for $\text{C}_{18}\text{H}_{26}\text{O}_5$: C 67.06%, H 8.13%, found: C 67.12%, H 8.13%.

(2R, 3S)-6-Hydroxy-2-methyltetrahydro -2H-pyran-3-yl pivalate (451)



A solution of CAN (1.86 g, 3.4 mmol) in water (2 mL) was added to a solution of ether **456** (545 mg) in acetonitrile (16 mL) and the resulting solution was stirred for a further 15 minutes. After this time the solution was diluted with ethyl acetate (20 mL) and the organic phase was separated, washed with water (2 x 10 mL), brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue chromatographed (2:1 hexanes/ethyl acetate) to deliver the title product as a colourless oil (306 mg, 84%) in a 1:0.8 (α : β) mixture of anomers; R_f : 0.33 (2:1 hexanes/ethyl acetate); IR: $\nu_{\max}$ 3420, 2973, 2865, 1730, 1481, 1280, 1155, 1059, 989; ^1H NMR (CDCl_3 , 400 MHz): δ 5.24 (s, 1H, α -anomer OCHOH), 4.82 (dd, $J_1 = 9.2$ Hz, $J_2 = 2.1$ Hz, 1H, β -anomer OCHOH), 4.48-4.38 (m, 2H, α - and β -anomer CHOPiv), 4.06 (dq, $J_1 = 9.6$ Hz, $J_2 = 6.3$ Hz, 1H, α -anomer H_3CCHO), 3.58 (dq, $J_1 = 9.3$ Hz, $J_2 = 2.1$ Hz, 1H, β -anomer H_3CCHO), 2.78 (br. s, 2H, α - and β -anomer CHOH), 2.00-1.79 (m, 6H, α - and β -anomer CH_2CH_2), 1.64-1.42 (m, 2H, α - and β -anomer CH_2CH_2), 1.19-1.17 (m, 9H, α - and β -anomer $\text{COC}(\text{CH}_3)_3$ and 3H, β -anomer H_3CCHO), 1.13 (d, $J = 6.4$ Hz, 3H, α -anomer H_3CCHO); ^{13}C NMR (CDCl_3 , 100 MHz): δ 177.66, 136.53, 95.80, 90.89, 73.54, 73.07, 72.27, 66.66, 38.73, 31.76, 29.11, 27.24, 27.03, 23.21, 18.05, 17.90; MS (CI, NH_3): m/z 215 $[\text{M}-\text{H}]^+$, 232 $[\text{M}-\text{H}+\text{NH}_4]^+$.

(2R, 3S)-6-Acetoxy-2-methyltetrahydro -2H-pyran-3-yl pivalate (452)



Acetic anhydride (323 μ L, 3.4 mmol) was added dropwise to a solution of hemiacetal **451** (246 mg, 1.1 mmol) in pyridine (138 μ L, 1.7 mmol) and dichloromethane (7 mL) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for a further 16 hours. After this time, saturated aqueous sodium hydrogen carbonate (5 mL), was added slowly, followed by water (10 mL). The organic phase was separated, washed with saturated aqueous copper (II) sulfate solution (2 x 10 mL), water (10 mL), brine (10 mL), dried over magnesium sulfate, concentrated under reduced pressure and the resulting residue was chromatographed (8:1 hexanes/ethyl acetate) to yield the title product as a colourless oil (223 mg, 76%) in a 1:3 (α : β) mixture of anomers; R_f : 0.33 (2:1 hexanes/ethyl acetate); IR: $\nu_{\max}$ 2976, 2874, 1728, 1368, 1217, 1155, 1036, 1005, 915; ^1H NMR (CDCl_3 , 400 MHz): δ 6.07 (s, 1H, α -anomer OCHOAc), 5.73 (dd, $J_1 = 9.2$ Hz, $J_2 = 2.4$ Hz, 1H, β -anomer OCHOAc), 4.52-4.42 (m, 2H, α - and β -anomer CHOPiv), 3.88 (dq, $J_1 = 9.8$ Hz, $J_2 = 6.2$ Hz, 1H, α -anomer H_3CCHO) 3.67 (dq, $J_1 = 8.8$ Hz, $J_2 = 6.2$ Hz, 1H, β -anomer H_3CCHO), 2.10 (s, 3H, α -anomer COCH_3), 2.09 (s, 3H, β -anomer COCH_3), 2.03-1.68 (m, 6H, α - and β -anomer CH_2CH_2), 1.58-1.48 (m, 2H, α - and β -anomer CH_2CH_2), 1.22-1.13 (m, 24H, α - and β -anomer $\text{COC}(\text{CH}_3)_3$ and H_3CCHO); ^{13}C NMR (CDCl_3 , 100 MHz): δ 177.59, 169.33, 93.590, 90.95, 74.14, 72.40, 71.65, 69.01, 38.72, 28.49, 28.00, 27.00, 26.33, 23.66, 21.13, 18.08, 17.84; MS (CI, NH_3): m/z 276 [$\text{M} + \text{NH}_4$] $^+$; HRMS (CI, NH_3) m/z calc. for $\text{C}_{13}\text{H}_{26}\text{NO}_5$ [$\text{M} + \text{NH}_4$] $^+$: 276.1811, found: 276.1815.

References

- (1) *Sherris Medical Microbiology* 4th ed.; Ryan K.J., R. C. G., Ed.; McGraw Hill, 2004.
- (2) Thomas, A. H. *J. Antimicrobial Chemotherapy* **1986**, *17*, 269.
- (3) Chu, M.; Yarborough, R.; Schwartz, J.; Patel, M. G.; Horan, A. C.; Gullo, V. P.; Das, P. R.; Puar, M. S. *J. Antibiot.* **1993**, *46*.
- (4) Rohr, J.; Thiericke, R. *Natural Prod. Reports* **1992**, *9*, 103.
- (5) Krohn, K.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 128.
- (6) Carreño, M. C.; Urbano, A. *Synlett* **2005**, *1*.
- (7) Rozek, T.; Janowski, W.; Hevko, J. M.; Tieknink, E. R. T.; Dua, S.; Stone, D. J. M.; Bowie, J. H. *Aust. J. Chem.* **1998**, *51*, 515.
- (8) Mal, D.; Roy, H. N.; Hazra, N. K.; Adhikari, S. *Tetrahedron* **1997**, *53*, 2177.
- (9) Mal, D.; Roy, H. N. *J. Chem. Soc. Perkin Trans. 1*, **1999**, 3167
- (10) Ghorai, S. K. R., H. N.; Bandopadhyay, M.; Mal, D. *J. Chem. Res. Synop.* **1999**, *30*.
- (11) Kraus, G. A.; Wan, Z. *Tetrahedron Lett.* **1997**, *38*, 6509.
- (12) Parker, K. A.; Ding, Q. *Tetrahedron* **2000**, *56*, 10249.
- (13) Murphy, W. S.; Neville, D.; Ferguson, G. *Tetrahedron Lett.* **1996**, *37*, 7615.
- (14) Heileman, M. J.; Tiedemann, R.; Moore, H. W. *J. Am. Chem. Soc.* **1998**, *120*, 3801.
- (15) Heileman, M. J.; Tiedemann, R.; Moore, H. W. *J. Org. Chem.* **1999**, 2170.
- (16) Hergueta, A. R.; Moore, H. W. *J. Org. Chem.* **2002**, *67*, 1388.
- (17) Kalogerakis, A.; Groth, U. *Org. Lett.* **2003**, *5*, 843.
- (18) Guingant, A.; Barreto, M. M. *Tetrahedron Lett.* **1987**, *28*, 3107.
- (19) Krohn, K.; Michael, J.; Zukowski, M. *Tetrahedron* **2000**, *56*, 4753.
- (20) Larsen, D. S.; O' Shea, M. D. *J. Chem. Soc. Perkin Trans. 1* **1995**, 1019.
- (21) Larsen, D. S.; O' Shea, M. D.; Broker, S. *Chem. Commun.* **1995**, 203.
- (22) Carreño, M. C.; Ribagorda, M.; Somoza, A.; Urbano, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 2755.
- (23) Matsuo, G. M., Y.; Nakata, M.; Matsumura, S.; Toshima, K. *J. Org. Chem.* **1999**, *64*, 7101

- (24) Matsumoto, T.; Sohma, T.; Yamaguchi, H.; Kurata, S.; Suzuki, K. *Tetrahedron* **1995**, *51*, 7347.
- (25) Matsumoto, T.; Sohma, T.; Yamaguchi, H.; Kurata, S.; Suzuki, K. *Synlett* **1995**, 263.
- (26) Kraus, G. A.; Zhang, N.; Melekhov, A.; Jensen, J. H. *Synlett* **2001**, 521.
- (27) Ayuwaka, S.; Takeuchi, T.; Sezaki, M.; Hara, T.; Umezawa, K.; Nagatsu, T. *J. Antibiotic*. **1968**, *21*, 350.
- (28) Nagatsu, T.; Ayuwaka, S.; Umezawa, K. *J. Antibiotic*. **1968**, *21*, 354.
- (29) Matsumoto, T.; Yamaguchi, H.; Hamura, T.; Tanabe, M.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 8383.
- (30) Yamaguchi, H.; Konegawa, T.; Tanabe, M.; Nakamura, T.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 8389.
- (31) Matsumoto, T.; Yamaguchi, H.; Tanabe, M.; Yasui, Y.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 8393.
- (32) Matsumoto, T.; Sohma, T.; Yamaguchi, H.; Suzuki, K. *Chem. Lett.* **1995**, *24*, 677.
- (33) Hoffmann, R. W. *Dehydrobenzene and cycloalkynes*; Academic Press: New York, 1967.
- (34) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem. Int. Ed.* **2003**, *42*, 502.
- (35) Wittig, G. *Angew. Chem.* **1965**, *77*, 752.
- (36) Heaney, H. *Chem. Rev.* **1962**, *62*, 81.
- (37) Hoffmann, R. W.; Viehe, H. G., Ed.; *Chemistry of Acetylenes*; Dekker: New York: 1969, p 1063.
- (38) Bryce, M. R.; Vernon, M.; Katritzky, A. R.; Boulton, A. J. *Adv. Het. Chem.* **1981**, *28*, 183.
- (39) Gilchrist, T. L. In *The chemistry of functional groups, Supplement C*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester: 1983, p 383.
- (40) Hart, H. In *The Chemistry of triple-bonded functional groups Supplement C2*; Patai, S., Ed.; Wiley: New York: 1994, p 1017.
- (41) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701.
- (42) Stoermer, R. K., B. *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 1633.
- (43) Fittig, R. *Liebigs Ann. Chem.* **1864**, *132*, 202.
- (44) Lüttringhaus, A.; v. Sääf, G. *Liebigs Ann. Chem.* **1939**, *542*, 241.

- (45) Morton, A. A.; Davidson, J. B.; Hakan, B. L. *J. Am. Chem. Soc.* **1942**, 64, 2242.
- (46) Wittig, G. *Naturwiss.* **1942**, 30, 696.
- (47) Roberts, J. D.; Simmons, H. E.; Carlsmith, L. A.; Vaughan, C. W. *J. Am. Chem. Soc.* **1953**, 75, 3290.
- (48) Roberts, J. D.; Semenow, D. A.; Simmons, H. E.; Carlsmith, L. A. *J. Am. Chem. Soc.* **1956**, 78, 601.
- (49) Panar, M.; Roberts, J. D. *J. Am. Chem. Soc.* **1960**, 82, 3629.
- (50) Husigen, R.; Rist, H. *Naturwiss.* **1954**, 41, 358.
- (51) Huisgen, R.; Knorr, R. *Tetrahedron Lett.* **1963**, 4, 1017.
- (52) Wittig, G.; Pohmer, L. *Angew. Chem.* **1955**, 67, 348.
- (53) Fisher, I. P.; Lossing, F. P. *J. Am. Chem. Soc.* **1963**, 85, 1018.
- (54) Berry, R. S.; Spokes, G. N.; Stiles, M. *J. Am. Chem. Soc.* **1962**, 84, 3570.
- (55) Berry, R. S.; Clardy, J.; Schafer, M. E. *J. Am. Chem. Soc.* **1964**, 86, 2738.
- (56) Chapman, O. L.; Mattes, K.; McIntosh, C. L.; Pacansky, J.; Calder, G. V.; Orr, G. *J. Am. Chem. Soc.* **1973**, 95, 6134.
- (57) Radziszewski, J. G.; Hess, B. A. J.; Zahradnik, R. *J. Am. Chem. Soc.* **1992**, 114, 52.
- (58) Warmuth, R. *Angew. Chem. Int. Ed.* **1997**, 36, 1347.
- (59) Wenthold, P. G.; Squires, R. R.; Lineberger, W. C. *J. Am. Chem. Soc.* **1998**, 120, 5279.
- (60) Jiao, H.; Schleyer, P. v. R.; Warmuth, R.; Houk, K. N.; Beno, B. R. *Angew. Chem. Int. Ed.* **1997**, 36, 2761.
- (61) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.
- (62) Kitamura, T.; Yamane, M.; Inoue, K.; Todaka, M.; Fukatsu, N.; Meng, Z.; Fujiwara, Y. *J. Am. Chem. Soc.* **1999**, 121, 11674.
- (63) Campbell, C. D.; Rees, C. W. *J. Chem. Soc. (C)* **1969**, 742.
- (64) Stiles, M.; Miller, R. G. *J. Am. Chem. Soc.* **1960**, 82, 3802.
- (65) Dockendorff, C.; Sahli, S.; Olsen, M.; Milhau, L.; Lautens, M. *J. Am. Chem. Soc.* **2005**, 127, 15028.
- (66) Wickham, P. P.; Hazen, K. H.; Guo, H.; Jones, G.; Reuter, K. H.; Scott, W. J. *J. Org. Chem.* **1991**, 56, 2045.
- (67) Fleming, I.; Mah, T. *J. Chem. Soc., Perk. Trans. 1* **1976**, 1577.

- (68) Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sakamoto, T.; Otani, Y.; Ohwada, T.; Kondo, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8514.
- (69) Wittig, G. *Org. Synth.* **1959**, *39*, 75.
- (70) Caster, K. C.; Keck, C. G.; Walls, R. D. *J. Org. Chem.* **2001**, *66*, 2932.
- (71) Coe, J. W.; Wirtz, M. C.; Bashore, C. G.; Candler, J. *Org. Lett.* **2004**, *6*, 1589.
- (72) Kawabata, H.; Nishino, T.; Nishiyama, Y.; Sonoda, N. *Tetrahedron Lett.* **2002**, *43*, 4911.
- (73) Nishiyama, Y.; Kawabata, H.; Nishino, T.; Hashimoto, K.; Sonoda, N. *Tetrahedron* **2003**, *59*, 6609.
- (74) LeHoullier, C. S.; Gribble, G. W. *J. Org. Chem.* **1983**, *48*, 1682.
- (75) Giles, R. G. F.; Hughes, A. B.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1581.
- (76) Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735.
- (77) Sapountzis, I.; Lin, W.; Fischer, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4364.
- (78) Biehl, E. R.; Nieh, E.; Hsu, K. C. *J. Org. Chem.* **1969**, *34*, 3595.
- (79) Larrosa, I.; Da Silva, M. I.; Gómez, P. M.; Hannen, P.; Ko, E.; Lenger, S. R.; Linke, S. R.; White, A. J. P.; Wilton, D.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2006**, *128*, 14042.
- (80) Peña, D.; Escudero, S.; Pérez, D.; Guitián, E.; Castedo, L. *Angew. Chem. Int. Ed.* **1998**, *37*, 2659.
- (81) Bromilow, J.; Brownlee, R. T. C.; Lopez, V. O.; Taft, R. W. *J. Org. Chem.* **1979**, *44*, 4766.
- (82) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004.
- (83) Matsumoto, T.; Yamaguchi, H.; Suzuki, K. *Synlett* **1996**, 433.
- (84) Matsumoto, T.; Sohma, T.; Yamaguchi, H.; Kurata, S.; Suzuki, K. *Tetrahedron* **1995**, *51*, 7347.
- (85) Matsumoto, T.; Sohma, T.; Yamaguchi, H.; Kurata, S.; Suzuki, K. *Synlett* **1995**, 263.
- (86) Young, S. D.; Coblens, K. E.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 4887.
- (87) Best, W. M.; Wege, D. *Aust. J. Chem.* **1986**, *39*, 635.
- (88) Best, W. M.; Wege, D. *Aust. J. Chem.* **1986**, *39*, 647.

- (89) Piggot, M. J.; Wege, D. *Aust. J. Chem.* **2000**, 53, 749.
- (90) Hurd, C. D.; Bonner, W. A. *J. Am. Chem. Soc.* **1945**, 67, 1664.
- (91) Kalvoda, L.; Farkaa, J.; Sorm, F. *Tetrahedron Lett.* **1970**, 2297.
- (92) Schmidt, R. R.; Hoffmann, M. *Tetrahedron Lett.* **1982**, 23, 409.
- (93) Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc.* **1985**, 107, 4289.
- (94) Kometani, T.; Kondo, H.; Fujimori, Y. *Synthesis* **1988**, 1005.
- (95) Matsumoto, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1988**, 29, 6935.
- (96) Hayashi, M.; Hashimoto, S.; Noyori, R. *Chem. Lett.* **1984**, 1747.
- (97) Matsumoto, T.; Katsuki, M.; Jona, H.; Suzuki, K. *J. Am. Chem. Soc.* **1991**, 113, 6982.
- (98) Kumazawa, T.; Onda, K.; Okuyama, H.; Matsuba, S.; Sato, S.; Onodera, J.-i. *Carbohydrate Res.* **2002**, 337, 1007.
- (99) Matsumoto, T.; Hosoya, T.; Suzuki, K. *Tetrahedron Lett.* **1990**, 31, 4629.
- (100) Toshima, K.; Matsuo, G.; Ishizuka, T.; Ushiki, Y.; Nakata, M.; Matsumura, S. *J. Org. Chem.* **1998**, 63, 2307.
- (101) Ben, A.; Yamauchi, T.; Matsumoto, T.; Suzuki, K. *Synlett* **2004**, 225.
- (102) Toshima, K. *Carbohydrate Res.* **2006**, 341, 1282.
- (103) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1.
- (104) Levy, D. E.; Tang, C. *The chemistry of C-glycosides*; Pergamon Press, Oxford, 1995.
- (105) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, 54, 9913.
- (106) W., L. D. Y.; He, M. S. *Curr. Top. Med. Chem.* **2005**, 5, 1333.
- (107) Reddy Dubbaka, S.; Steunenbergh, P.; Vogel, P. *Synlett* **2004**, 1235.
- (108) Denmark, S. E.; Regens, C. S.; Kobayashi, T. *J. Am. Chem. Soc.* **2007**, 129, 2774.
- (109) Denmark, S. E.; Kobayashi, T.; Regens, C. S. *Tetrahedron* **2010**, 66, 4745.
- (110) Bahnck, K. B.; Rychnovsky, S. D. *Chemical Commun.* **2006**, 2388.
- (111) Gong, H.; Gagné, M. R. *J. Am. Chem. Soc.* **2008**, 130, 12177.
- (112) Li, H.-H.; Ye, X.-S. *Org. and Biomol. Chem.* **2009**, 7, 3855.
- (113) Parker, K. A.; Su, D.-S. *J. Carb. Chem* **2005**, 46, 7271.
- (114) Kaliappan, K. P.; Subrahmanyam, A. V. *Org. Lett.* **2007**, 9, 1121.
- (115) Subrahmanyam, A. V.; Palanichamy, K.; Kaliappan, K. P. *Chem. Eur. J.* **2010**, 16, 8545.

- (116) Yamamoto, Y.; Saigoku, T.; Ohgai, T.; Nishiyama, H.; Itoh, K. *Chem. Commun.* **2004**, 2702.
- (117) Price, S.; Edwards, S.; Wu, T.; Minehan, T. *Tetrahedron Lett.* **2004**, 45, 5197.
- (118) Hauser, F. M.; Hu, X. *Org. Lett.* **2002**, 4, 977.
- (119) Kaelin, D. E.; Lopez, O. D.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, 123, 6937.
- (120) Woo, S.; Keay, B. A. *Synthesis* **1996**, 669.
- (121) Feng, C.-C.; Nandi, M.; Sambaiah, T.; Cheng, C.-H. *J. Org. Chem.* **1999**, 64, 3538.
- (122) Apsel, B.; Bender, J. A.; Escobar, M.; Kaelin Jr, D. E.; Lopez, O. D.; Martin, S. F. *Tetrahedron Lett.* **2003**, 44, 1075.
- (123) Kaelin, D. E.; Sparks, S. M.; Plake, H. R.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, 125, 12994.
- (124) Lautens, M.; Fagnou, K.; Yang, D. *J. Am. Chem. Soc.* **2003**, 125, 14884.
- (125) Barrett, A. G. M.; Head, J.; Smith, M. L.; Stock, N. S.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1999**, 64, 6005.
- (126) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, 2, 1694.
- (127) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. (C)* **1969**, 570.
- (128) Adejare, A.; Miller, D. D. *Tetrahedron Lett.* **1984**, 25, 5597.
- (129) Morton, G. E.; Barrett, A. G. M. *J. Org. Chem.* **2005**, 70, 3525.
- (130) Lau, J.; Pedersen, E. B.; Nielsen, C. M. *Acta Chem. Scand.* **1991**, 45, 616.
- (131) Sobhana Babu, B.; Kuppuswamy Balasubramanian, K. *Tetrahedron Lett.* **2000**, 41, 1271.
- (132) Morton, G. E.; Barrett, A. G. M. *Org. Lett.* **2006**, 8, 2859.
- (133) Hamura, T.; Hosoya, T.; Yamaguchi, H.; Kuriyama, Y.; Tanabe, M.; Miyamoto, M.; Yasui, Y.; Matsumoto, T.; Suzuki, K. *Helv. Chim. Acta*, **2002**, 85, 3589.
- (134) Petit, M.; Chouraqui, G.; Aubert, C.; Malacria, M. *Org. Lett.* **2003**, 5, 2037.
- (135) Seki, M.; Sakamoto, T.; Suemune, H.; Kanematsu, K. *J. Chem. Soc. Perkin Trans. 1* **1997**, 1707.
- (136) Glennon, R. A.; Young, R.; Benington, F.; Morin, R. D. *J. Med. Chem.* **1982**, 25, 1163.
- (137) Miles, W. H.; Berreth, C. L.; Smiley, P. M. *Tetrahedron Lett.* **1993**, 34, 5221.
- (138) Miles, W. H.; Connell, K. B. *Tetrahedron Lett.* **2003**, 44, 1161.

- (139) Lunniss, G. E., Ph.D Thesis, Imperial College, London, 2006.
- (140) Petit, M.; Chouraqui, G.; Auber, C.; Malacria, M. *Org. Lett.* **2003**, 5, 2037.
- (141) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, 21, 1357.
- (142) Maiti, B. C.; Musgrave, O. C.; Skoyles, D. *Tetrahedron* **2005**, 61, 1765.
- (143) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, 48, 1935.
- (144) Landi, J. J.; Ramig, K. *Synth. Commun.* **1991**, 21, 167.
- (145) Wheeler, A. S.; Naiman, B. *J. Am. Chem. Soc.* **1922**, 44, 2331.
- (146) Thomson, R. H. *J. Org. Chem.* **1948**, 13, 377.
- (147) Chorn, T. A.; Giles, R. G. F.; Green, I. R.; Hugo, V. I.; Mitchell, P. R. K.; Yorke, S. C. *J. Chem. Soc., Perk. Trans. 1* **1984**, 1339.
- (148) Qabaja, G.; Jones, G. B. *J. Org. Chem.* **2000**, 65, 7187.
- (149) Balasubramaniyan, V. *Chem. Rev.* **1966**, 66, 567.
- (150) Thomson, R. H. *J. Org. Chem.* **1948**, 13, 870.
- (151) Grunwell, J. R.; Karipides, A.; Wigal, C. T.; Heinzman, S. W.; Parlow, J.; Surso, J. A.; Clayton, L.; Fleitz, F. J.; Daffner, M.; Stevens, J. E. *J. Org. Chem.* **1991**, 56, 91.
- (152) Garden, J. F.; Thomson, R. H. *J. Chem. Soc. (Resumed)* **1957**, 2483.
- (153) Mawhinney, T. P.; Madson, M. A. *J. Org. Chem.* **1982**, 47, 3336.
- (154) Bakola-Christianopoulou, M. N.; Apazidou, K. K. *J. Org. Chem.* **1996**, 61, 1850.
- (155) Kampouris, E. M. *J. Chem. Soc. (C)* **1968**, 2125.
- (156) Hamura, T.; Arisawa, T.; Matsumoto, T.; Suzuki, K. *Angew. Chem. Int. Ed.* **2006**, 45, 6842.
- (157) Magnus, P.; Eisenbeis, S. A.; Fairhurst, R. A.; Iliadis, T.; Magnus, N. A.; Parry, D. *J. Am. Chem. Soc.* **1997**, 119, 5591.
- (158) Villeneuve, K.; Tam, W. *J. Am. Chem. Soc.* **2006**, 128, 3514.
- (159) Ballantine, M.; Menard, M. L.; Tam, W. *J. Org. Chem.* **2009**, 74, 7570.
- (160) Pihko, A. J.; Nicalaou, K. C.; P., K. A. M. *Tetrahedron: Asymm.* **2001**, 12, 937.
- (161) Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron* **2002**, 58, 6069.
- (162) Fraser-Reid, B.; Kelly, D. R. T., D. B.; Ravi, P.S. *J. Carbohydrate Chem.* **1983**, 2, 105.

- (163) Brimble, M.; Davey, R. M.; McLeod, M. D.; Murphy, M. *Aust. J. Chem.* **2003**, 56, 787.
- (164) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, 108, 303.
- (165) Chatgililoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1988**, 53, 3641.
- (166) Thiem, J.; Schneider, G.; Sinnwell, V. *Liebigs Ann. Chem.* **1986**, 814.
- (167) Peng, F.; Fan, B.; Shao, Z.; Pu, X.; Li, P.; Zhang, H. *Synthesis* **2008**, 3043.
- (168) Saquib, M.; Sagar, R.; Shaw, A. K. *Carbohydrate Res.* **2006**, 341, 1052.
- (169) Sobti, A.; Sulikowski, G. A. *Tetrahedron Lett.* **1994**, 35, 3661.
- (170) Sobti, A.; Kim, K.; Sulikowski, G. A. *J. Org. Chem.* **1996**, 61, 6.
- (171) Slafer, B.; Imperial College, London, unpublished results; 2010
- (172) Niemeier, O.; Imperial College, London; unpublished results; 2008.
- (173) Shan, M.; Xing, Y.; O' Doherty, G. A. *J. Org. Chem.* **2009**, 74, 5961.
- (174) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, 41, 1879.
- (175) Love, B. E.; Jones, E. G. *J. Org. Chem.* **1999**, 64, 3755.
- (176) Grunewald, G. L.; Kolar, A. J.; Palanki, M. S. S.; Paradkar, V. M.; Reitz, T. J.; Sall, D. *J. Org. Prep. Proc. Int.* **1990**, 22, 747.
- (177) Kim, A.; Powers, J. D.; Toczko, J. F. *J. Org. Chem.* **2006**, 71, 2170.
- (178) Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1988**, 110, 3296.
- (179) Parker, K. A.; Iqbal, T. *J. Org. Chem.* **1980**, 45, 1149.
- (180) de la Mare, P. B. D.; de la Mare, S.; Suzuki, H. *J. Chem. Soc. B* **1969**, 429.
- (181) Tietze, L. F.; Gericke, K. M.; Singidi, R. R. *Angew. Chem. Int. Ed.* **2006**, 45, 6990.
- (182) Dong, C.-G.; Hu, Q.-S. *Org. Lett.* **2006**, 8, 5057.
- (183) O'Connell, J. F.; Rapoport, H. *J. Org. Chem.* **1992**, 57, 4775.
- (184) Frydman, B.; Ojea, M. I. *Tetrahedron Lett.* **1998**, 39, 4765.
- (185) Wu, H.-J.; Yen, C.-H.; Chuang, C.-T. *J. Org. Chem.* **1998**, 63, 5064.
- (186) Herrlich, M.; Hampel, N.; Mayr, H. *Org. Lett.* **2001**, 3, 1629.
- (187) Kiss, J. *Carbohydrate Res.* **1969**, 11, 579.